Protocols for CPR Induced Consciousness

Saturday, November 14, 2015

To The Appointed EMS Advisory Board Members,

We are writing you today to introduce for your approval a new set of novel protocols for CPR Induced Consciousness. As you are well aware, Dean Cole, Dr. Rice, and the assistance of others, were successful in authoring a large grant that was approved by the Leona Helmsley Foundation for the deployment of LUCAS devices.

The combination of high quality CPR combined with the augmentation of a mechanical chest compression device (LUCAS) has caused Nebraska physicians and paramedics to begin experiencing increasing numbers of patients who are conscious while clinically dead. This situation requires we now consider the moral and ethical implications on how these patients should be treated.

Having a patient become combative while obtunded or fully aware of their surroundings while CPR is being performed on them can have profound emotional implications on the patient as well as the EMS crews caring for these patients. No one would ever consider taking a patient to surgery without anesthesia, yet in this remarkable new era, we may be doing this with patients who are undergoing cardiopulmonary resuscitation.

While the incidence of this situation is small, the total number of these cases are growing. As healthcare providers, we can no longer consider a patient in cardiac arrest to necessarily be clinically dead. To do so would be to ignore the patient's emotional state, dignity, and autonomy should they become conscious.

There is little written about this issue in literature. An exhaustive review (after eliminating cases which don't apply) only results in a dozen or so articles worldwide on this topic. Because of our rapid and massive deployment of LUCAS devices across the state of Nebraska, a situation has now occurred in which the world medical community at large has little to offer.

It is therefore our determination that Nebraska should be the first State in the country to adopt, approve, and suggest to the medical community our recommendations for how to manage and sedate a patient who becomes conscious while undergoing CPR.

We have researched literature from around the world and have included research from cardiologists and pharmacologists to extrapolate what we believe are the best guidelines to begin with. We humbly acknowledge as time and clinical cases grow, these guidelines will be most certainly revised and enhanced. It is the patient's well being, however, that compels us to make these recommendations today.

Attached to this cover letter is our final recommendations for the sedation protocols for patients who become conscious while undergoing CPR. As this is a new frontier, we are also attaching the literature we have searched including recommendations from invasive cardiologists and pharmacology reviews to justify our rationale for these protocols. We have made a deliberate and determined effort to be mindful of the complicated physiologic processes that are occurring in clinical death while simultaneously considering which drug combinations may have the best result at sedating while not compromising myocardial oxygen demand.

It is our intention to be present at the December EMS Board meeting to answer any questions as we submit these new protocols for inclusion in the EMS model protocols. Thank you for your time and consideration of the efforts put into this work.

Sincerely yours,

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Nebraska EMS Model Protocols
Adult Medical Protocols
CPR Induced Consciousness Sedation Protocol

ALL LEVELS

- Routine Assessment and Care
- Assess for signs of consciousness: Spontaneous eye opening, purposeful movement, verbal response to include moaning

EMR, EMT, AEMT

- Continue CPR
- If tiering is available, request ALS intercept

PARAMEDIC

- Administer Ketamine Bolus
  IV: 0.5-1.0 mg/kg
  IM: 2-3 mg/kg

- Consider co-administration of midazolam bolus*
  IV: 1mg
  IM: 2mg

- May repeat Ketamine bolus after 5-10 minutes if needed for continued sedation or if needed for continued sedation start infusion
  - IV bolus dose: 0.5-1.0 mg/kg OR IM: 2-3 mg/kg
  - IV infusion dose: 2-7 mcg/kg/minute

*Co-administration of benzodiazepines with ketamine has been suggested to decrease myocardial oxygen demand

REVIEW ARTICLE

Heart, Lung and Vessels. 2014; 6(4): 225-231

Anesthesia for cardiac catheterization procedures

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Heart, Lung and Vessels. 2014; 6(4): 225-231

ABSTRACT

Anesthesiologist's involvement for the purpose of diagnostic and interventional procedures in cardiac catheterization laboratory has been evolving particularly since last two decades. Catheterization laboratory environment poses certain challenges for the anesthesiologist including unfamiliar remote location, exposure to radiation, limited help from colleagues and communication with cardiologists. Anesthesiologists working in catheterization laboratory are required to have adequate knowledge of the environment, personnel, fluoroscope, echocardiography and type of radio contrast dye during the procedure. Anyone who is exposed to radiation environment is expected to protect himself from the exposure and must also wear a dosimeter for cumulative exposure tracing. There is no ideal anesthetic technique and the decision about sedation, general anesthesia or regional anesthesia for the procedure has to be made by attending anesthesiologists in consultation with cardiologists. Anesthesiologists should always try to minimize the effects of anesthesia on cardiovascular system. In addition, oxygenation and ventilatory management should be done according to the diagnostic procedure as it can also influence the diagnosis particularly in pediatric cath procedures. Since more complex procedures are being done in cardiac catheterization laboratory, it is the responsibility of anesthesia department to train and assign dedicated anesthesioloists for new challenges. Role of anesthetist should be well defined so that there is no confrontation during patient management. Sedation in cardiac catheterization laboratory by non-anesthetists is also an issue, which can be sorted out by making policies and protocol in consultation with cardiologists.

Keywords: *anesthesia, catheterization laboratory, cardiac.*

INTRODUCTION

Cardiac catheterization laboratory (CCL) procedures especially interventional procedures have increased exponentially over the last decade. First cardiac catheterization on human was introduced by Werner Forssmann (1) in 1929 who inserted a catheter through his own antecubital vein to the right heart. Nowadays extremely complex procedures are being performed in the cath. lab, sometimes entailing several hours.

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The catheterization laboratory environment is claustrophobic for anesthesiologists who are more comfortable working in the familiar environment that is the operating room. It is very important for anesthesiologist to become familiar (2) with the cath lab environment and communicate with cardiologist regarding patient management. Anesthesiologists face several challenges (3) while working in a remote location like the cath lab. These challenges include unfamiliarity with the surroundings, limited help from colleagues, insufficiency of drugs, radiation exposure and limited equipment.

General anesthesia considerations

CCL consists of a procedure room and a much smaller control station. The pro-

cedure room includes a procedure table, Fluoroscope, anesthesia machine, dye injecting equipment and different catheters and equipment necessary for the procedure. Control station has a glass window to provide a shield against radiation through which a technician can witness the whole procedure and also communicate through a mike speaker with cardiologist and other team members. There is also a computer workstation to record the findings of the procedure.

Communication with the cath. lab personnel (4) (nursing staff, technicians and cardiologist) and familiarity with anesthesia equipment is an essential component of the management. Cardiologist uses different routes of arterial and venous access (5) for the procedure. Furthermore, anesthetists need to be well aware of access point and related complications. Gas outlet, anesthesia machine, available medications and equipment all require particular attention. Some of the equipment may be different from main operating room. Every effort must be made to have the same standard equipment as in the main operating room for uniformity. Moreover drugs for intubation and resuscitation should always be prepared. Patients are mostly far away during the procedure therefore long intravenous tubings, long breathing circuits and long monitoring lines including end tidal carbon dioxide tubing are recommended. American Society of Anesthesiologist (ASA) has revised its standards for ventilation monitoring for moderate and deep sedation in 2011 and they have added end tidal carbon dioxide monitoring along with qualitative clinical signs.

During induction and intubation one must ensure that the cath. lab technician moves the fluoroscope from patient's head (6) so that airway can be secured. There are standard compact anesthesia machines also available for remote areas. Anesthesia technician must always be there to help. For prolonged cases a Foley catheter should be inserted. Naloxone and flumazenil should also be available to rescue the effects of narcotics and benzodiazepines.

Type of anesthesia

All types of anesthesia including monitored anesthesia care (MAC), general anesthesia and regional are provided in cath lab depending on the type of procedure. A discussion with cardiologist regarding the procedure and types of anesthesia is highly recommended. General anesthesia is the best option for new techniques and prolonged interventional procedures particularly those procedures in which the cessation of ventilation is required. Epidural anesthesia is beneficial in lower extremity stents procedures for vascular patency (7).

Most of the procedures in the cath lab can be performed under sedation. Mild sedation is commonly used by cardiologists with the help of nursing staff. A nurse or a physician must also assess and document patient's condition after each bolus of sedation according to the institutional guidelines (8). Unintentional progression from mild or moderate sedation to deep sedation is a possibility, particularly during propofol sedation in debilitated patients. Medical personnel using sedation, particularly deep sedation, should be well versed with the medications they use. Medical personnel must also be aware of the side effects and be able to manage the airway and haemodynamics. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) recommends that sedation practice, in an institution, should be supervised by anesthesia department (http://www.jointcommission.org/).

American Society of Anesthesiologists (ASA) statement in 2012 about granting privileges to non-anesthesiologist physicians for personally administering or su-

pervising deep sedation was that only qualified and trained non-anesthesiologists physicians can be given privileges for deep sedation. They should also be able to recognize and manage the complications. In our hospital, only Basic Life Support (BLS) certified medical staff can give mild sedation while for moderate to deep sedation the staff is necessitated to be Advanced cardiac life support (ACLS) certified. ASA standards for sedation are necessary to be implemented for all such procedures.

Percutaneous intervention (PCI)

PCI is usually performed under mild sedation under the supervision of a cardiologist. Anesthesiologists are usually required when patient is in respiratory distress or haemodynamically is unstable due to acute MI. In addition, cardiologist may decide to call anesthetist for rescue in conditions where cardiologist and team fail to sedate the patient, over-sedate the patient or in case of decompensated heart failure.

Proper intravenous access and airway management is the key for managing these patients. Intubation is always preferred over laryngeal mask airway (LMA). Invasive monitoring may be needed in certain situations. Close communication with the cardiologists is always helpful. Thrombosis is an acute complication during PCI.

Percutaneous closure of septal defect

Transesophageal echocardiography and general anesthesia with endotracheal intubation is commonly needed for atrial septal defect (ASD) and ventricular septal defect (VSD) closure. One has to be careful with transesophageal echocardiography probe manipulation because accidental extubation is a possibility. Arrhythmias, Atrioventricular (AV) conduction defect and device (Amplatzer) embolization are common complications. Post infarct VSD closure has also been tried with device.

Right heart dysfunction and pulmonary hypertension due to L-R shunt may worsen after closure of the defect. Echocardiography may help in early diagnosis and management.

Transcatheter cardiac valve stents

This percutaneous technique was introduced in 2002 for those valvular heart disease patients in whom surgical repair or replacement cannot be performed due to advanced age, comorbidities or technical difficulties. Retrograde transfemoral approach is commonly used for transcatheter aortic valve implantation (TAVI) but transapical and transaxillary (9) approaches have also been tried. Although general anesthesia is commonly used, noninvasive positive pressure ventilation (10) and deep sedation have also been tried successfully. Patients need to be adequately hydrated to prevent renal dysfunction due to intravenous contrast. Preparation for the procedure includes availability of blood, large bore intravenous lines, arterial line, central venous pressure and transesophageal probe insertion. Transventricular pacing wires are also placed for rapid ventricular pacing which helps in reducing the chances of valve migration. Hemodynamic goals during the TAVI procedure include: adequate preload and afterload, maintenance of sinus rhythm and avoidance of tachycardia. Norepinephrine infusion can be used for persistent hypotension (11) and regional anesthetic technique can be also an option for patients who require mini thoracotomy (12). Nitrous oxide is usually avoided during the procedure and patients can be extubated at the end of procedure. Furthermore it can be noted that anesthesiologists role is not only to manage haemodynamics during the procedure as they can also provide assistance during transesophageal echocardiography, which is an essential component of all aortic and mitral valve (13) procedures.

Electrophysiological studies

A discussion with cardiologist regarding the type of anesthesia is needed as most of the procedures can be done under moderate sedation. Haemodynamically significant tachyarrhythmias present before mapping are treated with cardioversion whereas antiarrhythmics are avoided. Deep sedation may be needed at the time of electrical cardioversion in certain procedures. Droperidol can depress accessory pathways conduction while opioids and barbiturates have been safely used in WPW syndrome (14). AV conduction through normal and accessory pathway can be depressed by volatile anesthetics halothane, isoflurane and enflurane (15). Sympathomimetic drugs should be avoided during ectopic foci mapping. Coughing, snoring and patients movements should be avoided during intra cardiac mapping. Dexmedetomidine may also interfere with elctrophysiological studies as it has shown to suppress supraventricular arrhythmias after congenital heart surgery (16).

High frequency jet ventilation (HFJV) has been used for atrial fibrillation ablation to reduce chest wall and lung movements, along with reduction in left atrial volume changes. HFJV not only reduces procedure time, but also leads to improved outcomes (17, 18). Total intravenous anesthesia should be used for maintenance with this technique.

Patients coming for catheter-based procedure for ventricular arrhythmias usually have underlying coronary artery disease (CAD), severe LV dysfunction and are on multiple drugs, which can interact with anesthetics. Particularly, caution is needed with amiodarone and its potential side effects of hypothyroidism, hypotension and bradycardia. Temporary pacemakers should be available as these patients may not respond to atropine (19, 20). General anesthesia with endotracheal tube is usually chosen due to prolong cases and patient's condition. Volatile anesthetics have variable effect (21) while opioids have no effect on inducing ventricular tachycardia (VT) (22).

Implantable cardioverter defibrillator (ICD)

These patients are usually very sick, have multiple comorbidities and have history of myocardial infarction, ventricular tachycardia and ventricular fibrillation. They may not be able to remain in supine position for a long period of time. Device can be placed percutaneously under mild to moderate sedation (23) but device testing by delivering shocks requires deep sedation or general anesthesia. Nurse based deep sedation has also been tried to reduce the cost of the procedure but it increases the use of narcotic reversals agents (24).

External defibrillator adhesive pads must always be placed on the patient's chest. These are used for inducing ventricular fibrillation and at the same time as back up for defibrillation in case of ICD failure. Pacing may be also required as bradycardia may follow defibrillation. Testing is not always needed at the time of insertion and can be omitted in high risk patients. Arterial line is usually not required except in unstable patients.

Complications related to procedure include cardiac perforation, myocardial injury(25), stroke and pneumothorax due to subclavian venous access. Furthermore, refractory hypotension is a possibility after repeated shocks (26).

Radiation exposure

Healthcare workers are exposed to radiation during fluoroscopy (27) which can cause damaging effects such as dermal necrosis, cellular mutation, cancer and birth defects. It has carcinogenic effect on brain, skin and thyroid. Prolonged exposures can

lead to infertility. Exposure to radiation is measured by roentgen equivalent man (rem). Normal chest X-ray delivers 40 milirem (mrem) per examination. Anyone who is exposed to radiation environment should wear a dosimeter for cumulative exposure tracing. Two monitoring badges are mainly recommended by International commission on radiation protection, one under the lead apron and second on the collar. A fetal monitor is recommended for pregnant health care worker (28). Centre of Disease Control (CDC) supports the principle of ALARA (As low as reasonably possible) for radiation exposure and several centres are using protocols (29). Occupational limit of radiation exposure must not exceed 5 rem per calendar year (30).

Anesthesiologists and other healthcare personnel should minimize radiation exposure by adhering to three basic principles: firstly, keeping a maximum possible distance from radiation source; secondly, minimizing the exposure time; thirdly, shielding by wearing the lead aprons, thyroid collar ad shielded gloves. Acrylic stands and leaded glasses can also be used for protection. Anesthesiologist should depend more on infusion techniques for sedation and general anesthesia so that they can stay away from the radiation source. Intermittent intravenous boluses during the procedure increases the chances of radiation dose (31). 18% of the active bone marrow is still exposed to the effects of radiation even with proper lead apparel.

Radio contrast dye

Two types of contrast dyes are used in cardiovascular imaging studies. Classification of these dyes depends on their dissociation (ionic) and non dissociation (Nonionic) in a solution. Incidence of adverse reaction with ionic dye is 5.65% (32) while nonionic agents are relatively less toxic. Electrocardiography (ECG) changes and vasodilation is more pronounced with ionic agents. Nonionic dyes can be safely given to the patients who developed anaphylactoid reaction to ionic contrast in previous studies. Commonly used nonionic contrasts are Iohexol (Omnipaque), Iopamidol (Isovue) and Ioxilan (Oxilan).

Pre-procedure orders should clearly mention six hours fasting after light meal and two hours of clear liquid so that patient is adequately hydrated. Contrast administration in a patient with impaired renal function can lead to further impairment (33). Nephrotoxicity depends on the amount of contrast reaching the renal arteries so cardiologist should try to limit the dose. Prolonged and multiple studies can be performed in stages by giving a gap of 72 hrs. For the prevention of contrast induced nephropathy, avoidance of high osmolar contrast media and administration of adequate hydration (34) before and after the procedure is recommended. Acetylcysteine is not recommended by ACC/AHA for contrast induced nephropathy (8).

Pediatric cardiac procedures

Pediatric cath procedures are different from adults in several ways including different types of disease pattern in the patient, different requirements for the procedure, mandatory sedation or GA in almost all patients and a need of complete evaluation of structurally abnormal heart. Commonly performed procedures are angioplasty, valvuloplasty, coil embolization, atrial septostomy, device closure and electrophysiological studies. Right heart catheterization is commonly done in CHD patients for evaluation of shunting, oxygenation and pressures in different chambers and pulmonary vascular resistance. Bennett (35) et al. have reported the incidence of cardiac arrest and death during the procedure 0.49% and 0.08% respectively. These complications are much higher in those patients who

have supra systemic pulmonary hypertension (36, 37). There is no ideal anesthetic technique and the decision about sedation or general anesthesia for the procedure has to be made by attending anesthesiologists in consultation with cardiologists. General anesthesia is mainly chosen in critically ill patients, prolonged procedures, uncooperative patients and in procedures which require transesophageal echocardiography.

Midazolam is commonly used for premedication and during the procedure. Cardiologist and nursing staff feel comfortable with the use of midazolam and fentanyl for mild to moderate sedation. Advantages of midazolam include short duration, minimal effects on haemodynamics and respiration and reversibility with flumazenil. Over sedation with premedication and during the procedure may lead to hypercarbia, hypoxemia, airway obstruction and exaggerated pulmonary hypertension (HTN).

Ketamine has several advantages over other anesthetics as it maintains respiration and hemodynamics, provides analgesia and at the same time it keeps the patient sedated and motionless for the procedure. There is however some controversy regarding its effect on pulmonary vascular resistance. Williams et al. (38) used ketamine safely with sevoflurane in pulmonary HTN patients. It has also been used in combination with midazolam and propofol to counteract its side effects of cardiovascular stimulation and emergence reaction (39).

Generally, FiO2 is reduced to around 25 % or below when checking SaO2 in different chambers of the heart. Higher FiO2 during the procedure may change the pulmonary vascular resistance measurements. Blood should be cross-matched and available in those interventional procedures where there is a possibility of uncontrolled bleeding. Anesthesiologists should be particularly careful in removing air from all the intravenous tubings.

CONCLUSION

It is quite clear that the number of procedures and their complexities have increased in the cardiac catheterization laboratory. Furthermore, an increase in interventional procedures performed on very sick patient can be foreseen. The role of anesthesiologist has become more challenging in this changing environment. Anesthesia departments should plan ahead to cope with this growing population by allocating the trained staff and by developing policies according to the procedure and type of anesthesia. Furthermore, communication and planning in consultation with the cardiology department can facilitate patient care in this remote location.

Although cardiologist and nursing staff in certain cases can provide sedation in the catheterization laboratory, policies for sedation should be made and should be strictly implemented by both departments.

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Cite this article as: Hamid M. Anesthesia for cardiac catheterization procedures. Heart, Lung and Vessels. 2014; 6(4): 225-231.
Source of Support: Nil. **Disclosures:** None declared.

Resuscitation 85 (2014) 1799–1805

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical Paper

AWARE—AWAreness during REsuscitation—A prospective study☆

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ARTICLE INFO

Article history:
Received 28 June 2014
Received in revised form 2 September 2014
Accepted 7 September 2014

Keywords:
Cardiac arrest
Consciousness
Awareness
Near death experiences
Out of body experiences
Post traumatic stress disorder
Implicit memory
Explicit memory

ABSTRACT

Background: Cardiac arrest (CA) survivors experience cognitive deficits including post-traumatic stress disorder (PTSD). It is unclear whether these are related to cognitive/mental experiences and awareness during CPR. Despite anecdotal reports the broad range of cognitive/mental experiences and awareness associated with CPR has not been systematically studied.

Methods: The incidence and validity of awareness together with the range, characteristics and themes relating to memories/cognitive processes during CA was investigated through a 4 year multi-center observational study using a three stage quantitative and qualitative interview system. The feasibility of objectively testing the accuracy of claims of visual and auditory awareness was examined using specific tests. The outcome measures were (1) awareness/memories during CA and (2) objective verification of claims of awareness using specific tests.

Results: Among 2060 CA events, 140 survivors completed stage 1 interviews, while 101 of 140 patients completed stage 2 interviews. 46% had memories with 7 major cognitive themes: fear; animals/plants; bright light; violence/persecution; deja-vu; family; recalling events post-CA and 9% had NDEs, while 2% described awareness with explicit recall of 'seeing' and 'hearing' actual events related to their resuscitation. One had a verifiable period of conscious awareness during which time cerebral function was not expected.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.09.004.

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http://dx.doi.org/10.1016/j.resuscitation.2014.09.004
0300-9572/

Conclusions: CA survivors commonly experience a broad range of cognitive themes, with 2% exhibiting full awareness. This supports other recent studies that have indicated consciousness may be present despite clinically undetectable consciousness. This together with fearful experiences may contribute to PTSD and other cognitive deficits post CA.

1. Introduction

The observation that successful cardiac arrest (CA) resuscitation is associated with a number of psychological and cognitive outcomes including post-traumatic stress disorder, depression and memory loss as well as specific mental processes that may share some similarities with awareness during anaesthesia,[1,2] has raised the possibility that awareness may also occur during resuscitation from CA.[3] In addition to auditory perceptions, which are characteristic of awareness during anesthesia, CA survivors have also reported experiencing vivid visual perceptions, characterized by the perceived ability to observe and recall actual events occurring around them.[4] Although awareness during anesthesia is associated with dream like states, the specific mental experience described in association with CA is unknown. CA patients have reported visual perceptions together with cognitive and mental activity including thought processes, reasoning and memory formation.[3] Patients have also been reported to recall specific details relating to events that were occurring during resuscitation.[4]

Although there have been many anecdotal reports of this phenomenon, only a handful of studies have used rigorous research methodology to examine the mental state that is associated with CA resuscitation.[4–7] These studies have examined the scientifically imprecise yet commonly used term of 'near-death experiences' (NDE).[3] While NDE have been reported by 10% of CA survivors,[3] the overall broader cognitive/mental experiences associated with CA, as well as awareness, and the association between actual CA events and auditory/visual recollection of events has not been studied. The primary aim of this study was to examine the incidence of awareness and the broad range of mental experiences during resuscitation. The secondary aim was to investigate the feasibility of establishing a novel methodology to test the accuracy of reports of visual and auditory perception and awareness during CA.

2. Methods

In this multicenter observational study, methods were initially pilot tested at 5 hospitals prior to study start-up (01/2007–06/2008) at which point the study team recruited 15 US, UK and Austrian hospitals (out of an original selected group of 25) to participate in data collection. Between 07/2008 and 12/2012 the first group of CA patients were enrolled in the AWARE study. These patients were identified using a local paging system that alerted staff to CA events. CA patients were eligible for study participation if they met the following inclusion criteria:

- CA as defined by cessation of heartbeat and respiration (in-hospital or out-of-hospital with on-going cardiopulmonary resuscitation (CPR) on arrival at the emergency department (ED)).
- Age > 18 years.
- Surviving patients deemed fit for interview by their physicians and caregivers.
- Surviving patients providing informed consent to participation.

When possible, interviews were completed by a research nurse or physician while the CA survivor was still an inpatient. The interviewers all underwent dedicated training regarding the interview methodology by the study chief/principle investigator. Informed consent was obtained when patients were deemed medically fit to complete an in-person interview prior to discharge. For patients who could not be interviewed during their hospital stay, a telephone interview protocol was established to consent and interview these patients by telephone to minimize losses to follow up. Given the severity of the condition, the study provided for a large proportion of patients being unable to participate due to ill health in the sample size calculations.

The study received ethical approval at each participating site prior to the start of data collection. Following advice from the ethics committee, a protocol was implemented to avoid contacting individuals not interviewed during their hospital stay who died after hospital discharge. Death registries and letters to the patients' doctors requesting permission to contact their patients were implemented to identify patients who either died or should not be contacted. If no objections or concerns were raised and patients were still alive after discharge, a member of the original clinical team sent an introductory letter together with a stamped addressed envelope requesting permission to contact patients for the study who were missed while in hospital. For these patients who agreed to be contacted, a member of the research team, obtained informed consent, and completed data collection via the telephone. However due to the severity of the medical condition (and in particular the differing levels of physical impairment) combined with the requirements set forth by the ethics committee for contacting patients (outlined above), the time to telephone interviews following hospital discharge was between 3 months and 1 year. All in-hospital interviews were carried out prior to discharge. These took place between 3 days and 4 weeks after cardiac arrest depending on the severity of the patients' critical illness.

To assess the accuracy of claims of visual awareness (VA) during CA, each hospital installed between 50 and 100 shelves in areas where CA resuscitation was deemed likely to occur (e.g. emergency department, acute medical wards). Each shelf contained one image only visible from above the shelf (these were different and included a combination of nationalistic and religious symbols, people, animals, and major newspaper headlines). These images were installed to permit evaluation of VA claims described in prior accounts.[4] These include the perception of being able to observe their own CA resuscitation from a vantage point above. It was postulated that should a large proportion of patients describe VA combined with the perception of being able to observe events from a vantage point above, the shelves could be used to potentially test the validity of such claims (as the images were only visible if looking down from the ceiling).[1] Considering these perceptions may be occurring after brain function has returned following resuscitation, we

[1] Some researchers have proposed such recollections and perceptions are likely illusory. This method was proposed as a tool to test this particular hypothesis. We considered this to be important as despite widespread interest no studies had objectively tested this claim. It was considered that should a large group of patients with VA and the ability to observe events from above consistently fail to identify the images, this could support the hypothesis that the experiences had occurred through a different mechanism (such as illusions) to that perceived by the patients themselves.

also installed a different image (triangle) on the underside of each shelf to test the accuracy of VA based on the possibility that patients could have looked upwards after CA recovery or had their eyes open during CA.

Using a three stage interview process, patients were asked general and focused questions about their remembrances during cardiac arrest. Stage 1 of the interviews included demographic questions as well as general questions on the perception of awareness and memories during CA. Stage 2 interviews probed further into the nature of the experiences using scripted open ended questions and the 16 item Greyson NDE scale.[8] This validated NDE scale was used to define NDE's in this study. For each of the 16 items in the NDE scale, responses were scored 0 (not present), 1 (weakly present) or 2 (strongly present). Out of a possible maximum score of 32, a NDE was considered present with a score of ≥7, while experiences <7 are not compatible with NDE.[8] Patients with detailed auditory and visual recollections relating to their period of cardiac arrest were flagged for a further in-depth interview (stage 3) to obtain details of their experience. This later interview was conducted by the study principal investigator (PI).

Using both the qualitative and quantitative data, patients' memories and experiences were initially classified into 2 broad categories:

(1) No perception of awareness and/or memories.
(2) Perception of awareness and/or memories.
Based on patient's responses to the NDE scale the second category was subdivided into three further categories.
(3) Detailed non-NDE memories without recall and awareness of CA events.
(4) Detailed NDE memories without recall and awareness of CA events.
(5) Detailed NDE memories with detailed auditory and/or VA with recall of CA events.

In order to evaluate auditory recollections we proposed a protocol to introduce "auditory stimuli" during CA similar to those used in studies of implicit learning during anaesthesia.[9] During the pilot testing phase, staff were asked to mention the names of three specific cities or colors and evaluate the survivors' ability to recall these through explicit or implicit memory recall, however unlike the relatively controlled environment of anesthesia, staff found it impractical to administer these stimuli and this was therefore not carried forward to the main study. Patients who claimed to have had visual and auditory awareness (category 5 above) whether identified in hospital or during the telephone interview were invited to complete an in-depth interview conducted by the study principal investigator to obtain more details of their experiences.

Both quantitative and qualitative data were analyzed in a descriptive manner. Potential confounders such as age, gender and time to interview were evaluated. Summaries of the scripted interviews were reviewed and responses grouped based upon themes identified. Potential differences in demographic characteristics between reporting groups was evaluated. Age was compared using two sample t-test or Wilcoxon's rank sum test when sample sizes were small. Gender was compared using chi-square test or Fisher's exact test when sample sizes were small. Statistical analysis was carried out using StatXact-9 (Cytel Inc., Cambridge, MA) and SAS 9.3 (SAS Institute Inc., Cary, NC).

3. Results

A total of 2060 CA events were recorded with an average 16% ($n = 330$) overall survival to hospital discharge. Of the 330 survivors, 140 patients were found eligible, provided informed consent, and were interviewed. Fifty-two interviews were completed in-hospital and 90 after discharge. Two patients refused interview and the remaining 188 patients either did not meet inclusion criteria, died after hospital discharge, were not deemed suitable for further follow up by their physicians, or did not respond to the invitation letters for a telephone follow up. A summary of study participation and outcomes is reported in Fig. 1. From the 140 patients completing stage 1 of the interview process, 101 patients (72%) went on to complete stage 2 interviews. The 39 patients unable to complete both stages did so predominantly due to fatigue.

Among those interviewed 67% ($n = 95$) were men. The mean age (±SD) was 64 ± 13 years (range 21–94). After stage 1 interview 61% (85/140) of patients reported no perception of awareness or memories (category 1). Although no patient demonstrated clinical signs of consciousness during CPR as assessed by the absence of eye opening response, motor response, verbal response whether spontaneously or in response to pain (chest compressions) with a resultant Glasgow Coma Scale Score of 3/15, nonetheless 39% (55/140) (category 2) responded positively to the question "Do you remember anything from the time during your unconsciousness". There were no significant differences with respect to age or gender between these two groups.

Among the 101 patients who completed stage 2 interviews, no differences existed by age or gender. Responses to the NDE scale are summarized in Table 1 and 46 (46%) confirmed having had no recall, awareness or memories. The remaining 55 of 101 patients with perceived awareness or memories (category 2) were subdivided further. Forty-six described memories incompatible with a NDE

Table 1
Responses to the Greyson NDE Scale[a] (number and percent responding positively to each of the 16 scale questions[b]).

Question	n	%
(1) Did you have the impression that everything happened faster or slower than usual?	27	27
(2) Were your thoughts speeded up?	7	7
(3) Did scenes from your past come back to you?	5	5
(4) Did you suddenly seem to understand everything?	6	6
(5) Did you have a feeling of peace or pleasantness?	22	22
(6) Did you have a feeling of joy?	9	9
(7) Did you feel a sense of harmony or unity with the universe?	5	5
(8) Did you see, or feel surrounded by, a brilliant light?	7	7
(9) Were your senses more vivid than usual?	13	13
(10) Did you seem to be aware of things going on that normally should have been out of sight from your actual point of view as if by extrasensory perception?	7	7
(11) Did scenes from the future come to you?	0	0
(12) Did you feel separated from your body?	13	13
(13) Did you seem to enter some other, unearthly world?	7	7
(14) Did you seem to encounter a mystical being or presence, or hear an unidentifiable voice?	8	8
(15) Did you see deceased or religious spirits?	3	3
(16) Did you come to a border or point of no return?	8	8

$n = 101$. Mean Greyson score ± SD = 2.02 ± 3.71. Score range = 0–22.
[a] The total is based upon individuals completing the instrument (101/142, 72%).
[b] A positive response was defined as responses of either weakly or strongly present for each item.

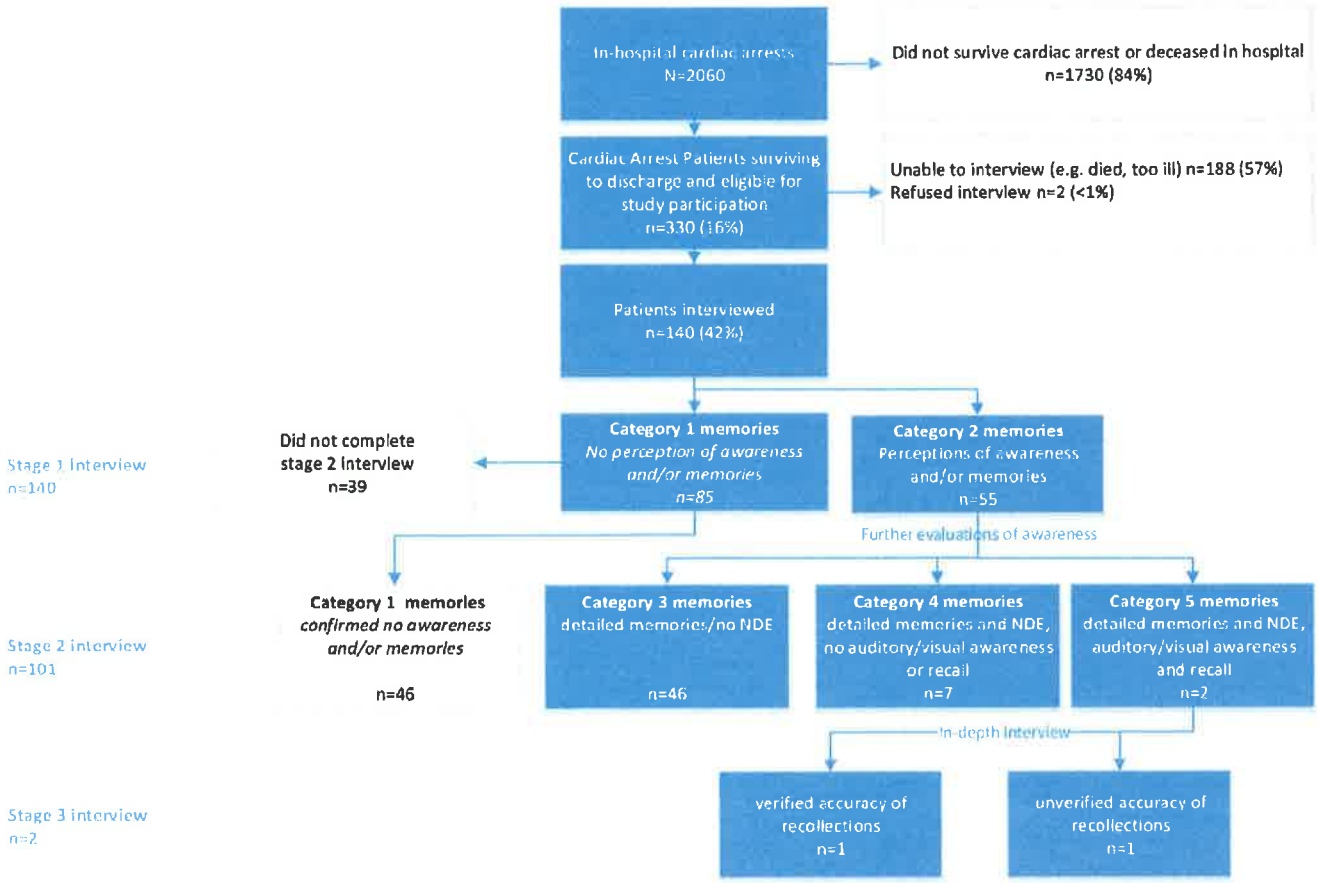

Fig. 1. Summary of study enrollment and outcomes.

and without recall of CA events (median NDE score = 2) (IQR = 3) (category 3). The remaining 9 of 101 patients (9%) had experiences compatible with NDE's. Seven (7%) had no auditory or visual recall of CA events (median NDE scale score = 10 (IQR = 4), highest NDE score 22) (category 4). The detailed NDE account from one patient in this group is summarized in Table 2. The other two patients (2%) experienced specific auditory/visual awareness (category 5). Both patients had suffered ventricular fibrillation (VF) in non-acute areas where shelves had not been placed. Their descriptions are summarized in Table 2. Both were contacted for further in-depth interviews to verify their experiences against documented CA events. One was unable to follow up due to ill health. The other, a 57 year old man described the perception of observing events from the top corner of the room and continued to experience a sensation of looking down from above. He accurately described people, sounds, and activities from his resuscitation (Table 2 provides quotes from this interview). His medical records corroborated his accounts and specifically supported his descriptions and the use of an automated external defibrillator (AED). Based on current AED algorithms, this likely corresponded with up to 3 min of conscious awareness during CA and CPR.[2] As both CA events had occurred in non-acute areas without shelves further analysis of the accuracy of VA based on the ability to visualize the images above or below the shelf was not possible. Despite the installation of approximately 1000 shelves across the participating hospitals only 22% of CA events actually took place in the critical and acute medical wards where the shelves had been installed and consequently over 78% of CA events took place in rooms without a shelf.

While NDE's provided a quantifiable measure of a patients' cognitive recollections in relation to CA, using our CA survivor interview transcripts as part of stage 2 interviews, we evaluated the narratives of patients' memory's without NDE's (NDE scale < 7). Although prior studies had by enlarge focused on the occurrence of NDE's in CA only, however our observation that other cognitive themes aside from NDE's also exist in CA led to an evaluation of the narratives for other specific themes. Narratives were categorized into 7 themes: (1) fear; (2) animals and plants; (3) a bright light; (4) violence or a feeling of being persecuted; (5) deja vu experiences; (6) seeing family; (7) recalling events that likely occurred after recovery from CA. Narratives are presented in Table 3 by theme.

4. Discussion

Our data suggest that CA patients may experience a range of cognitive processes that relate both to the CA and post-resuscitation periods. Although, the relatively high proportion of patients who perceived having memories and awareness was unexpected and should be confirmed through future research, the fact that the observed frequency of NDE (9%) in our study was consistent with reports from prior studies (approximately 10%),[4–7] may provide some measure of internal validity for this observation.

The finding that conscious awareness may be present during CA is intriguing and supports other recent studies that have indicated consciousness may be present in patients despite clinically

[2] After the recognition of a first shockable rhythm, the built in AED algorithms require at least 2 min of CPR before a further rhythm check is followed by a second defibrillation attempt if advised. Adding in time for analysis of the rhythm and defibrillation it is likely the period of CA would have been at least 3 min.

Table 2
Categories 4 and 5 recollections from structured interviews.

Category 4 recollections
"I have come back from the other side of life. . .God sent (me) back, it was not (my) time—(I) had many things to do. . .(I traveled) through a tunnel toward a very strong light, which didn't dazzle or hurt (my) eyes. . .there were other people in the tunnel whom (I) did not recognize. When (I) emerged (I) described a very beautiful crystal city. . . there was a river that ran through the middle of the city (with) the most crystal clear waters. There were many people, without faces, who were washing in the waters. . .the people were very beautiful. . . there was the most beautiful singing. . .(and I was) moved to tears. (My) next recollection was looking up at a doctor doing chest compressions".
Category 5 recollections
Recollection # 1
(Before the cardiac arrest) "I was answering (the nurse), but I could also feel a real hard pressure on my groin. I could feel the pressure, couldn't feel the pain or anything like that, just real hard pressure, like someone was really pushing down on me. And I was still talking to (the nurse) and then all of a sudden, I wasn't. I must have (blanked out). . .but then I can remember vividly an automated voice saying, "shock the patient, shock the patient," and with that, up in (the) corner of the room there was a (woman) beckoning me. . .I can remember thinking to myself, "I can't get up there". . .she beckoned me. . . I felt that she knew me, I felt that I could trust her, and I felt she was there for a reason and I didn't know what that was. . .and the next second, I was up there, looking down at me, the nurse, and another man who had a bald head. . .I couldn't see his face but I could see the back of his body. He was quite a chunky fella. . . He had blue scrubs on, and he had a blue hat, but I could tell he didn't have any hair, because of where the hat was.
The next thing I remember is waking up on (the) bed. And (the nurse) said to me: "Oh you nodded off. . .you are back with us now." Whether she said those words, whether that automated voice really happened, I don't know. . .. I can remember feeling quite euphoric. . .
I know who (the man with the blue had was). . .I (didn't) know his full name, but. . .he was the man that. . .(I saw) the next day. . .I saw this man [come to visit me] and I knew who I had seen the day before."
Post-script – Medical record review confirmed the use of the AED, the medical team present during the cardiac arrest and the role the identified "man" played in responding to the cardiac arrest.
Recollection # 2
"At the beginning, I think, I heard the nurse say 'dial 444 cardiac arrest'. I felt scared. I was on the ceiling looking down. I saw a nurse that I did not know beforehand who I saw after the event. I could see my body and saw everything at once. I saw my blood pressure being taken whilst the doctor was putting something down my throat. I saw a nurse pumping on my chest. . .I saw blood gases and blood sugar levels being taken."

Table 3
Major non-NDE cognitive themes recalled by patients following cardiac arrest.

Fear
"I was terrified. I was told I was going to die and the quickest way was to say the last short word I could remember"
"Being dragged through deep water with a big ring and I hate swimming—it was horrid".
"I felt scared"
Animals and plants
"All plants, no flowers".
"Saw lions and tigers".
Bright light
"The sun was shining"
"Recalled seeing a golden flash of light"
Family
"Family talking 10 or so. Not being able to talk to them"
"My family (son, daughter, son-in-law and wife) came"
Being persecuted or experiencing violence
"Being dragged through deep water"
"This whole event seemed full of violence and I am not a violent man, it was out of character".
"I had to go through a ceremony and . . . the ceremony was to get burned. There were 4 men with me, whichever lied would die. . .. I saw men in coffins being buried upright.
Deja vu experiences
". . .experienced a sense of De-ja vu and felt like knew what people were going to do before they did it after the arrest. This lasted about 3 days"
Events occurring after initial recovery from cardiac arrest
Experienced . . ."a tooth coming out when tube was removed from my mouth"

undetectable consciousness.[9–15] For instance, implicit learning with the absence of explicit recall has been demonstrated in patients with undetectable consciousness,[9–13] while others have demonstrated conscious awareness during persistent vegetative states (PVS).[14,15] As the relative contribution of implicit learning and memory in CA is unknown it remains unclear whether the recalled experiences reflect the totality of patients' experiences or simply the tip of a deeper iceberg of experiences not recalled through explicit memory. It is intriguing to consider whether patients may have greater conscious activity during CA (and whether this and fearful experiences may impact the occurrence of PTSD) than is evident through explicit recall, perhaps due to the impact of post-resuscitation global cerebral inflammation and/or sedatives on memory consolidation and recall. However, the results of this and other studies (outlined above) raise the possibility that additional assessments may be needed to complement currently used clinical tests of consciousness and awareness.

Although the etiology of awareness during CA is unknown, the results of our study and in particular our verified case of VA suggest it may be dissimilar to awareness during anesthesia. While some investigators have hypothesized there may be a brief surge of electrical activity after cardiac standstill,[16] in contrast to anesthesia typically there is no measurable brain function within seconds after cardiac standstill.[17–21] This 'flatlined' isoelectric brain state which occurs with CA onset usually continues throughout CPR since insufficient cerebral blood flow (CBF) is achieved[22] to meet cerebral metabolic requirements during conventional CPR.[23–25] However it was estimated our patient maintained awareness for a number of minutes into CA. While certain deep coma states may lead to a selective absence of cortical electrical activity in the presence of deeper brain activity,[26] this seems unlikely during CA as this condition is associated with global rather than selective cortical hypoperfusion as evidenced by the loss of brain stem function. Thus, within a model that assumes a causative relationship between cortical activity and consciousness the occurrence of mental processes and the ability to accurately describe events during CA as occurred in our verified case of VA when cerebral function is ordinarily absent or at best severely impaired is perplexing.[27] This is particularly the case as reductions in CBF typically lead to delirium followed by coma, rather than an accurate and lucid mental state.[28]

Despite many anecdotal reports and recent studies supporting the occurrence of NDE's and possible VA during CA, this was the first large-scale study to investigate the frequency of awareness, while attempting to correlate patients' claims of VA with events that occurred during cardiac arrest. While the low incidence (2%) of explicit recall of VA impaired our ability to use images to objectively examine the validity of specific claims associated with VA, nonetheless our verified case of VA suggests conscious awareness may occur beyond the first 20–30 s after CA (when some residual brain electrical activity may occur)[16] while providing a quantifiable time period of awareness after the brain ordinarily reaches an isolectric state.[17–21] The case indicates the experience likely occurred during CA rather than after recovery from CA or before CA. No CBF would be expected since unlike ventricular tachycardia, VF is incompatible with cardiac contractility particularly after CPR has stopped during a rhythm check.[29] Although, similar experiences have been categorized using the scientifically undefined and imprecise term of out of body experiences (OBE's), and further categorized as autoscopy and optical illusions,[30–32] our study suggests that VA and veridical

perception during CA are dissimilar to autoscopy since patients did not describe seeing their own double.[4–7] Furthermore as hallucinations refer to experiences that do not correspond with objective reality, our findings do not suggest that VA in CA is likely to be hallucinatory or illusory since the recollections corresponded with actual verified events. Our results also highlight limitations with the categorization of experiences in relation to CA as hallucinatory,[33] particularly as the reality of human experience is not determined neurologically.[34,35] Although alterations in specific neuro modulators involved with every day "real" experiences can also lead to illusions or hallucinations, however this does not prove or disprove the reality of any specific experience whether it be love, NDE's or otherwise.[34,35] In fact the reality of any experience and the meaning associated with it is determined socially (rather than neurologically) through a social process whereby humans determine and ascribe meaning to phenomenon and experience within any given culture or society (including scientific groups and societies).[34–35]

Our results provide further understanding of the broad mental experience that likely accompanies death after circulatory standstill. As most patients' experiences were incompatible with a NDE, the term NDE while commonly used may be insufficient to describe the experience that is associated with the biological processes of death after circulatory standstill. Future research should focus on the mental state of CA and its impact on the lives of survivors as well as its relationship with cognitive deficits including PTSD. Our data also suggest, the experience of CA may be distinguished from the term NDE, which has many scientific limitations including a lack of a universally accepted physiological definition of being 'near death'.[34–36] This imprecision may contribute to ongoing conflicting views within the scientific community regarding the subject.[36–39]

Our study had a number of limitations including the fact that we were unable to ascertain whether patients' response to the question of having memories during CA (in category 1) truly reflected a perception of having memories or possibly difficulties with understanding the question. An additional limitation was the limited number of patients with explicit recall of CA events whose memories could have been further analyzed. Furthermore owing to the acuity and severity of the critical illness associated with CA, the time to interview for patients was invariably not exactly the same for every patient, which may have introduced biases (such as recall bias and confabulation) in the recollections. While pre-placement of visual targets in resuscitation areas aimed at testing VA was feasible from a practical viewpoint (there were no reported adverse incidents), the observation that 78% of CA events took place in areas without shelves illustrates the challenge in objectively testing the claims of VA in CA using our proposed methodology. It also suggests that a different and more refined methodology may be needed to provide an objective visual target to examine the mechanism of VA and the perceived ability to observe events during CA. Although in this study the potential role of cofounders such as age, gender and time to interview were evaluated, our results indicated a wide variation in these variables. Consequently a larger study would be warranted to further explore the relationship between these variables with VA. Such a study should also explore the impact of variables that may impact the quality of cerebral blood flow and cerebral recovery such as the duration of CA, quality of CPR during CA, location of CA (in-hospital versus out-of hospital), underlying rhythm, use of hypothermia during CA and after ROSC.

5. Conclusions

CA survivors experience a broad range of memories following CPR including fearful and persecutory experiences as well as awareness. While explicit recall of VA is rare, it is unclear whether these experiences contribute to later PTSD. Studies are also needed to delineate the role of explicit and implicit memory following CA and the impact of this phenomenon on the occurrence of PTSD and other life adjustments among CA survivors.

Conflict of interest statement

None of the authors have any conflicts of interest to declare.

Financial support

Resuscitation Council (UK), Nour Foundation, Bial Foundation. Researchers worked independent of the funding bodies and the study sponsor. Furthermore, the study sponsor did not participate in study design, analysis and interpretation of results or the writing of the manuscript.

Ethical approval

This study obtained ethics approvals from each participating center prior to the start of recruitment and data collection. Each surviving patient gave informed consent prior to their being interviewed.

Data sharing

All authors either had access to all the data or the opportunity to review all data.

Transparency declaration

I Sam Parnia as lead author affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Acknowledgements

We acknowledge the Biostatistical Consultation and support from the Biostatistical Consulting Core at the School of Medicine, Stony Brook University as well as the help of Dr's Ramkrishna Ramnauth, Vikas Kaura, Markand Patel, Jasper Bondad, Markand Patel, Georgina Spencer, Jade Tomlin, Rav Kaur Shah, Rebecca Garrett, Laura Wilson, Ismaa Khan, and Jade Tomlin with the study.

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Ketamine

Drug Description

Ketamine is a sedative hypnotic used to provide anesthesia for short diagnostic and surgical procedures, as an inducing agent, as an adjunct to supplement low-potency anesthetics such as nitrous oxide, and as a supplement to local and regional anesthesia. Ketamine produces an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally transient, minimal respiratory depression. Ketamine is similar in structure, mechanism of action, and activity to phencyclidine (PCP), but ketamine is much less potent and has a shorter duration of action. Ketamine has been associated with substance abuse and illicit use, and some abusers report effects superior to those of PCP or LSD. Reportedly, ketamine has been used to facilitate rape (i.e., acquaintance or date rape) because the drug can be easily administered in beverages to unknowing victims. Slang terms for ketamine include K, Special K, Keets, Green, Jet, Super Acid, and Super C.[26474] Ketamine received FDA approval in 1970. Ketamine is also widely used in veterinary medicine.

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Classifications

Anesthetics

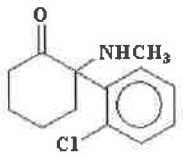
General Anesthetics

Brand Names

- Ketalar

Chemical Structures

Ketamine
$C_{13}H_{16}ClNO$



Mechanism of Action

Mechanism of Action: Ketamine induces sedation, immobility, amnesia, and marked analgesia. Ketamine-induced analgesia is obtained without the induction of deep levels of anesthesia. Increasing doses of ketamine result in anesthesia. The state of unconsciousness it produces is trancelike (eyes may remain open until deep anesthesia is obtained) and cataleptic in nature and has been referred to as dissociative anesthesia due to the strong feeling of dissociation from the environment that is experienced by the subject receiving the drug. Ketamine appears to selectively interrupt association pathways of the brain before producing somatesthetic sensory blockade. It may selectively depress the thalamoneocortical system before significantly obtunding more ancient cerebral centers and pathways. Unlike barbiturates that act on the reticular activating system in the brainstem, ketamine acts on receptors in the cortex and limbic system. Ketamine non-competitively blocks N-methyl-D-aspartate (NMDA) receptors. The activity on NMDA receptors may be responsible for the analgesic as well as psychiatric (psychosis) effects of ketamine. Ketamine has a sympathomimetic activity resulting in tachycardia, hypertension, increased myocardial and cerebral oxygen consumption, increased cerebral blood flow, and increased intracranial and intraocular pressure. Ketamine is a potent bronchodilator and can be used to treat refractory bronchospasm. Clinical effects observed following ketamine administration include increased blood pressure, increased muscle tone (may resemble catatonia), opening of eyes (usually accompanied by nystagmus), increased myocardial oxygen consumption, and minimal respiratory depression. Ketamine has no effects on pharyngeal or laryngeal reflexes, thus, the patient's airway remains intact.

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Pharmacokinetics

Pharmacokinetics: Ketamine is administered parenterally. When used illicitly, ketamine may be snorted, smoked, swallowed, or

injected. Ketamine readily crosses the placenta and is rapidly distributed into highly perfused tissues (e.g., heart, lung, and brain), followed by muscle and peripheral tissues, and then fat. The distribution phase lasts about 45 minutes, with a half life of 10—15 minutes, which corresponds clinically to the anesthetic effect of the drug. The elimination half-life of ketamine is about 2—3 hours. Metabolites are excreted renally (90%) and fecally (5%), with 4% of an administered dose excreted unchanged in urine.

•Route-Specific Pharmacokinetics

Oral Route

The oral bioavailability of ketamine is 16%. Amnesia about events that occur during drug exposure begins within 15—20 minutes after oral ketamine ingestion, and abrupt loss of consciousness may occur.

Intravenous Route

When administered intravenously, a sensation of dissociation occurs in 15 seconds, and anesthesia occurs within 30 seconds. Anesthesia lasts 5 to 10 minutes for IV administration. The analgesic effects of ketamine last from 20—45 minutes. The anesthetic effects are terminated by a combination of redistribution and hepatic biotransformation to an active metabolite, which is about one-third as active as ketamine in reducing halothane MAC requirements.

Intramuscular Route

Following IM injection, ketamine is rapidly absorbed. Anesthesia occurs in 3—4 minutes and lasts 12—25 minutes for IM administration.

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Indications

Labeled

- general anesthesia induction
- general anesthesia maintenance

Off-Label, Recommended

- acute bronchospasm †
- sedation induction †
- severe pain †
- status asthmaticus †

† Off-label indication

For general anesthesia induction:

NOTE: As with other general anesthetic agents, the individual response to ketamine is somewhat varied depending on the dose, administration route, and patient age; dosage recommendations cannot be absolutely fixed. Titrate the ketamine dose according to the patient's requirements.[43431]

NOTE: Ketamine hydrochloride injection is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine hydrochloride injection is best suited for short procedures but it can be used, with additional doses, for longer procedures.[43431]

NOTE: Ketamine is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained. The regimen of a reduced dose of ketamine supplemented with diazepam can be used to produce balanced anesthesia by combination with other agents such as nitrous oxide and oxygen.[43431]

Intravenous dosage:

Adults and Adolescents >= 16 years: 1—4.5 mg/kg IV slowly over 60 seconds. On average, 2 mg/kg will produce 5—10 minutes of surgical anesthesia. If a longer effect is desired, additional increments can be administered IV to maintain anesthesia without producing significant cumulative effects. Alternatively, in adults, 1—2 mg/kg IV may be given at a rate of 0.5 mg/kg/min for induction in combination with diazepam (2—5 mg IV given in a separate syringe over 60 seconds). In most cases, diazepam doses of <= 15 mg IV will be sufficient. The occurrence of an emergence reaction may be less with the combination.[43431]

Infants†, Children†, and Adolescents < 16 years†: 1—2 mg/kg IV has been recommended as an induction agent for anesthesia in pediatric patients by some experts.[43459]

Neonates: Safety and efficacy have not been established.

Intramuscular dosage:

Adults and Adolescents >= 16 years: 6.5—13 mg/kg IM. Approximately 10 mg/kg will usually produce 12—25 minutes of surgical anesthesia. If a longer effect is desired, additional increments can be administered intramuscularly to maintain anesthesia without producing significant cumulative effects.[43431]

Infants†, Children†, and Adolescents < 16 years†: 3—4 mg/kg IM has been recommended as an induction agent for anesthesia in pediatric patients by some experts.[43459]

Neonates: Safety and efficacy have not been established.

For general anesthesia maintenance:
NOTE: As with other general anesthetic agents, the individual response to ketamine is somewhat varied depending on the dose, administration route, and patient age; dosage recommendations cannot be absolutely fixed. Titrate the ketamine dose according to the patient's requirements. Adjust the maintenance dose according to the patient's anesthetic needs and whether an additional anesthetic agent is employed.[43431]
NOTE: Purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.[43431]
Intravenous dosage:
Adults and Adolescents >= 16 years: Increments of one-half to the full induction dose (i.e. 0.5—4.5 mg/kg) IV over 60 seconds and repeated as needed. Adults induced with ketamine augmented with intravenous diazepam may be maintained on a ketamine infusion of 0.1—0.5 mg/minute. The dose of diazepam is 2—5 mg IV as needed (usually not more than 20 mg diazepam IV for combined induction and maintenance will be sufficient). The occurrence of an emergence reaction may be less with the combination.[43431]
Neonates, Infants, Children, and Adolescents < 16 years: Safety and efficacy have not been established.
Intramuscular dosage:
Adults and Adolescents >= 16 years: Increments of one-half to the full induction dose (i.e. 3.25—13 mg/kg) IM as needed may be used for maintenance.[43431]
Neonates, Infants, Children, and Adolescents < 16 years: Safety and efficacy have not been established.

For preprocedure sedation induction† (minor procedures):
Oral dosage:
Children: 6—10 mg/kg PO (mixed in cola or other beverage) given 30 minutes before procedure.
Intravenous dosage:
Children: Usual dosage is 0.5—1 mg/kg IV (range: 0.5—2 mg/kg). Do not exceed 0.5 mg/kg/min or administer any dose faster than over 60 seconds.

For the treatment of acute respiratory failure† associated with refractory acute bronchospasm† due to respiratory syncytial virus (RSV) infection†, pneumonia†, or status asthmaticus† in patients who are mechanically ventilated:
NOTE: Adjunctive treatment of a moderately severe asthma exacerbations with ketamine did not cause significant clinical improvement in either adults (bolus of 0.1 mg/kg and infusion of 0.5 mg/kg/hour for 3 hours) or children (bolus of 0.2 mg/kg and infusion of 0.5 mg/kg/hour for 2 hours) who were treated in the emergency department and were not intubated.[32135] [32136]
Intravenous dosage:
Children and Adolescents: 2 mg/kg IV bolus then 0.02—0.06 mg/kg/minute (mean of 0.032 +/- 0.01 mg/kg/minute) continuous infusion (mean duration of 40 +/- 31 hours) plus their preexisting bronchodilatory regimen led to significantly improved gas exchange and dynamic compliance of the chest in 17 intubated patients ages 5 months to 17 years. For example, the PaO_2/FIO_2 ratio increased significantly from 116 +/- 55 before ketamine to 174 +/-82, 269 +/-151, and 248 +/-124 at 1, 8, and 24 hours respectively, after ketamine initiation. All patients received at least 24 hours of traditional bronchodilatory treatment before ketamine initiation and were successfully weaned from mechanical ventilation.[32134]

For the treatment of refractory severe pain†:
Intravenous dosage:
Adults: 10—50 mg/hour IV for severe pain associated with complex regional pain syndrome led to complete pain relief in 25 of 33 patients. An additional 6 patients had partial pain relief. The mean infusion duration was 4.7 days (range, 0.75—20 days). Twelve of the 33 patients relapsed and received another dose of ketamine that caused complete relief for all patients. Furthermore, 7 of the 12 patients maintained complete relief for at least a year.[32142] In another study, significant improvements in pain relief, as determined by use of the Brief Pain Inventory, occurred in patients with severe ischemic limb pain who got opioids and a single infusion of 0.6 mg/kg of ketamine as compared with patients who only got opioids.[32143] A single dose of ketamine 0.25 mg/kg or 0.5 mg/kg was also effective for patients with cancer and neuropathic pain who were already taking morphine.[32145]
Children: 0.1 mg/kg/hour IV for severe pain due to metastatic neuroblastoma improved pain in a 2.8 year-old girl. After 6 days, the infusion was increased to 0.2 mg/kg/hour in combination with a morphine infusion, which adequately maintained pain control until her death 3 weeks after ketamine initiation.[32146] In another case, severe neuropathic pain from glioblastoma multiforme in a 12-year-old was reduced by the addition of a ketamine infusion 36—410 mg/24 hours to a morphine infusion until her death 67 days after ketamine initiation.[32147]

Maximum Dosage Limits
•Adults
Specific maximum dosage information is not available. Dosage must be individualized.
•Elderly
Specific maximum dosage information is not available. Dosage must be individualized.
•Adolescents
Specific maximum dosage information is not available. Dosage must be individualized.
•Children
Specific maximum dosage information is not available. Dosage must be individualized.

Patients with Hepatic Impairment Dosing
Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Patients with Renal Impairment Dosing
Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

†Off-label indication

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Administration Information

General Administration Information
For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Injectable Administration

- Ketamine is administered intramuscularly or intravenously.
- Because of rapid induction after intravenous injection, the patient should be in a supported position during administration.
- To prevent vomiting and aspiration, administer ketamine on an empty stomach.
- Monitor heart rate, respiratory rate, and blood pressure during IV use.
- Do not mix ketamine and diazepam or barbiturates in the same syringe.
- Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit. Color of solution may vary from colorless to very slightly yellowish and may darken upon prolonged exposure to light. Darkening does not affect potency, but do not use if a precipitate appears.

Intravenous Administration
Direct IV injection

- Dilute the desired dose of the 100 mg/mL concentration with equal parts of sterile water for injection, 0.9% sodium chloride injection, or 5% Dextrose injection. Do not inject the 100 mg/mL concentration of ketamine intravenously without proper dilution.
- Inject intravenously over 60 seconds. More rapid injection can cause respiratory depression or an enhanced pressor response.

Continuous IV infusion

- Dilute 10 mL of the 50 mg/mL injection or 5 mL of the 100 mg/mL injection in 500 mL of 0.9% sodium chloride injection or 5% dextrose injection and mix well. The resultant infusion solution should contain 1 mg/mL of ketamine. If fluid restriction is necessary, 250 mL of diluent may be used to give a concentration of 2 mg/mL.
- Infuse intravenously at a rate of 1—2 mg/minute. Titrate rate based on patient response. The development of tonic-clonic movements during ketamine anesthesia does not necessitate a dosage increase.

Intramuscular Administration

- No dilution necessary.
- Inject into a large muscle mass. Aspirate prior to injection to avoid injection into a blood vessel.

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Contraindications / Precautions

Absolute contraindications are italicized

- *head trauma*
- *hypertension*
- *intracranial bleeding*
- *intracranial mass*
- heart failure
- hypovolemia
- increased intracranial pressure
- increased intraocular pressure

- *myocardial infarction*
- *stroke*
- alcoholism
- angina
- breast-feeding
- cardiac disease
- children
- coronary artery disease
- dehydration
- driving or operating machinery
- ethanol intoxication
- females
- geriatric
- glaucoma
- head and neck anesthesia
- infants
- intravenous administration
- labor
- neonates
- obstetric delivery
- ocular surgery
- ocular trauma
- pain
- pregnancy
- psychosis
- schizophrenia
- substance abuse
- thyrotoxicosis
- vomiting

Ketamine is contraindicated in patients in whom a significant elevation of blood pressure would constitute a serious hazard, such as those patients with *hypertension, stroke, head trauma* or *intracranial mass,* or *intracranial bleeding.* Similarly, ketamine should be used with caution in patients with increased intracranial pressure or increased intraocular pressure (e.g., glaucoma) because these pressures may increase significantly after a single dose of ketamine. Carefully evaluate patients with ocular trauma or space occupying lesions (i.e., brain neoplasms) prior to administration of ketamine. Ketamine should be used cautiously in ocular surgery. Because of the substantial increase in myocardial oxygen consumption, ketamine should be used with caution in patients with hypovolemia, dehydration, or cardiac disease, especially coronary artery disease (e.g., angina, congestive heart failure, and *myocardial infarction*).

Emergence reactions (see Adverse Reactions) are more common in adolescents and adults 15—45 years of age, in females, following short procedures, large doses (> 2 mg/kg), or after rapid administration (> 40 mg/min). These reactions are less frequent when the drug is given by intramuscular administration and if lower doses of ketamine are used in conjunction with diazepam during induction and maintenance of anesthesia. These reactions may be reduced if verbal, tactile, and visual stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs. Outpatient surgery patients should not be released until recovery is complete and should be accompanied by a caregiver. Patients should be instructed to avoid driving or operating machinery for at least 24 hours or until they have recovered from the effects of the anesthesia.

Use ketamine with caution in patients with chronic alcoholism or acute ethanol intoxication.

Ketamine must be administered slowly over at least 60 seconds; more rapid intravenous administration can result in respiratory depression, apnea, and enhanced pressor response.

During surgical procedures involving visceral pain pathways, ketamine should be supplemented with an agent that manages visceral pain (e.g., opiate agonist).

Because ketamine can cause psychosis and exacerbate symptoms of chronic schizophrenics, it should be used with caution in patients with psychiatric disorders, such as schizophrenia or acute psychosis.

Substance abuse of ketamine has been reported. Physical dependence, tolerance, and a withdrawal syndrome have been reported with long-term ketamine use (see Adverse Reactions). Illicit drug use of ketamine for its psychological effects (i.e., similar to PCP) and use as 'date rape' drug due to its amnestic effects has been reported.

Use ketamine with caution in patients with a history of thyrotoxicosis because they are at an increased risk of developing tachycardia and hypertension due to ketamine-induced cardiac stimulation.

Use with caution for head and neck anesthesia during surgical procedures of the pharynx, larynx, or trachea because ketamine increases salivary and tracheal-bronchial secretions and usually does not suppress pharyngeal and laryngeal reflexes. Ketamine should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if ketamine is used alone. Give atropine, scopolamine or other drying agent prior to induction of anesthesia.

Vomiting has been reported following ketamine administration. Intact laryngeal-pharyngeal reflexes may offer some protection, however the possibility of aspiration must be considered due to the use of supplemental anesthetics and muscle relaxants.

Ketamine has not been assigned a specific pregnancy category by the FDA. According to the manufacturer, safe use of ketamine during pregnancy, labor, and obstetric delivery has not been established and such use is not recommended.[43431]

The elimination half-life of ketamine is short (2.5 hours).[43431] The drug should be undetectable in the mother's plasma approximately 11 hours after a dose, and therefore, it is unlikely that breast-feeding would pose a significant risk to the infant at this time.[49597] It may be prudent to consider an alternate form of feeding (e.g., using stored breast milk) during the drug elimination period to minimize infant exposure. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Ketamine dose selection for a geriatric patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

The safety and efficacy of ketamine have not been established in neonates, infants, or children < 16 years of age [43431]; however, ketamine has been used off-label for anesthesia induction and analgesia in pediatric patients.[43459]

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Pregnancy / Breast-feeding

Ketamine has not been assigned a specific pregnancy category by the FDA. According to the manufacturer, safe use of ketamine during pregnancy, labor, and obstetric delivery has not been established and such use is not recommended.[43431]

The elimination half-life of ketamine is short (2.5 hours).[43431] The drug should be undetectable in the mother's plasma approximately 11 hours after a dose, and therefore, it is unlikely that breast-feeding would pose a significant risk to the infant at this time.[49597] It may be prudent to consider an alternate form of feeding (e.g., using stored breast milk) during the drug elimination period to minimize infant exposure. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

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Interactions

Level 1 - Severe

- Monoamine oxidase inhibitors (MAOIs)
- St. John's Wort, Hypericum perforatum

Level 2 - Major

- Ethanol
- General Anesthetics

Level 3 - Moderate

- Antihypertensive Agents
- Anxiolytics, Sedatives, and Hypnotics
- Memantine
- Opiate agonists
- Phenothiazines
- Pregabalin
- Sedating H1-blockers
- Skeletal Muscle Relaxants
- Theophylline, Aminophylline
- Thyroid hormones
- Tubocurarine

Level 4 - Minor

Ketamine may potentiate the neuromuscular blocking effects of tubocurarine, including prolonged respiratory depression with apnea.[7095] The use of ketamine and local or general anesthetics is possible when an adequate respiratory exchange is maintained.[7093] The use of halogenated anesthetics concomitantly with ketamine can lengthen the elimination half-life of ketamine and delay recovery from anesthesia. Concurrent use of ketamine (especially in high doses or when rapidly administered) with halogenated anesthetics can increase the risk of developing bradycardia, hypotension, or decreased cardiac output.

The use of ketamine with other CNS depressants (e.g., ethanol [6341], phenothiazines, sedating H1-blockers, or skeletal muscle relaxants) can potentiate CNS depression and/or increase the risk of developing respiratory depression.[6892] [7095] Reduced doses of ketamine may be required with concurrent administration of other anxiolytics, sedatives, and hypnotics. Prolonged recovery time may occur if barbiturates and/or opiate agonists are used concurrently with ketamine.[7093] Ketamine has been reported to

antagonize the hypnotic effect of thiopental. However, low doses of benzodiazepines or rapidly acting barbiturates may be used to prevent or treat emergence reactions to ketamine.

The coadministration of ketamine and levothyroxine has been reported to cause marked hypertension and tachycardia.[43942] Use caution when coadministering ketamine with thyroid hormones.

Ketamine may be associated with hypotension; however the frequency is less than with inhalational anesthetic agents.[6892] Concomitant use of antihypertensive agents and ketamine may increase the risk of developing hypotension.

When ketamine and theophylline are given concurrently a clinically significant reduction in the seizure threshold is observed. Unpredictable extensor-type seizures have been reported with concurrent administration of these agents.[7097]

St. John's wort, Hypericum perforatum, may intensify or prolong the effects of general anesthetics; profound hypotension has also been reported. In one report, the authors recommend that patients should discontinue taking St. John's Wort at least 5 days prior to anesthesia.[5566] The American Society of Anesthesiologists has recommended that patients stop taking herbal medications at least 2—3 weeks before surgery to decrease the risk of adverse reactions.[4936] [5568]

Ketamine is a NMDA antagonist and may lead to additive adverse effects if combined with memantine, also an NMDA antagonist. It may be prudent to avoid coadministration of ketamine with memantine. If coadministration cannot be avoided, monitor for increased adverse effects such as agitation, dizziness and other CNS events.[8204]

The concomitant use of pregabalin with ketamine may augment the CNS depressant effect of pregabalin.[7523]

Patients receiving monoamine oxidase inhibitors (MAOIs) may have an increased risk of hypotension after administration of general anesthetics, although specific studies are not available.[8837] Combined hypotensive effects are also possible with the combined use of MAOIs and spinal anesthetics.[4673] [5595] Phenelzine, tranylcypromine, and transdermal selegiline are contraindicated for use for at least 10 days prior to elective surgery.[4673] [6398] [8837]

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Adverse Reactions

- amnesia
- anorexia
- anxiety
- apnea
- bradycardia
- delirium
- diplopia
- dysphoria
- erythema
- hallucinations
- hypersalivation
- hypertension
- hypotension
- insomnia
- involuntary movements
- laryngospasm
- maculopapular rash
- nausea
- nightmares
- nystagmus
- psychological dependence
- psychosis
- respiratory depression
- sinus tachycardia
- tolerance
- vomiting
- withdrawal

Cardiovascular side effects of ketamine include (in order of decreasing frequency): hypertension and sinus tachycardia, hypotension and sinus bradycardia, and other cardiac arrhythmias (rare). Elevation of blood pressure begins shortly after ketamine injection, reaches maximum levels within a few minutes, and usually returns to preanesthetic levels within 15 minutes of injection. In the majority of cases, the systolic and diastolic blood pressure peaks from 10—50% above baseline shortly after induction, but the elevation can be higher and longer in some patients. The arrhythmogenic effects of ketamine are controversial. In some experiments, ketamine abolishes epinephrine-induced arrhythmias by prolonging the relative refractory period, and in others, ketamine sensitizes the myocardium to catecholamines and enhances the arrhythmogenicity of epinephrine. Ketamine increases myocardial oxygen consumption and there is a risk of myocardial ischemia in patients with coronary artery disease if ketamine is used alone. However, ketamine in combination with midazolam, diazepam, or sufentanil is well-tolerated in patients undergoing coronary artery bypass surgery.

Respiratory depression and apnea have been reported and are more likely to occur following rapid administration or high doses of ketamine. Laryngospasm and other forms of airway obstruction are rare but can occur.

Nausea/vomiting, hypersalivation, injection site reaction, erythema, maculopapular rash (morbilliform), and anorexia have also been

reported, although they are rare adverse reactions to ketamine.

Diplopia and nystagmus have been noted following ketamine administration. Slightly increased intraocular pressure may also be noted.

In patients receiving ketamine, CNS and psychological adverse effects can occur in as many as 12% of patients and include visual hallucinations, nightmares or illusions, and post-anesthesia emergence delirium (often consisting of dissociative or floating sensations). These reactions occur more frequently in patients between 15 and 45 years of age and typically last only a few hours, although some patients may experience flashbacks several weeks postoperatively. Pretreatment with benzodiazepines decreases the incidence of emergence reactions. Outpatients should not be released until recovery is complete and should be accompanied by a caregiver. Ketamine has been reported being used as a drug of abuse leading psychological dependence. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, anxiety, dysphoria, disorientation, insomnia, flashbacks, hallucinations, and psychosis. Users of ketamine describe sensations of floating to being separated from their bodies. Some ketamine experiences involve a feeling of almost complete sensory detachment that is likened to a near-death experience. These experiences are sometimes referred to as the "K-hole" and are similar to a "bad trip" on LSD. Ketamine physical dependence and tolerance are possible following prolonged administration. A withdrawal syndrome with psychotic features has been described following discontinuation of long-term ketamine use. There have been reports of flashbacks occurring weeks after recovery. Ketamine causes amnesia and abrupt loss of consciousness and is odorless and tasteless, which allows it to be added beverages without being detected. These properties have led it to be used as a "date rape" drug.[26474]

Tonic/clonic movements, which can resemble seizures, have occurred with ketamine use. These involuntary movements are believed to result from enhanced skeletal muscle tone.

Revision Date: 1/28/2010 9:01:00 AM

Legend
Click result icon for detailed study information.
C = Compatible
I = Incompatible
= Results uncertain, variable or dependent on conditions
ND = No Data Available

From Trissel's 2™ Clinical Pharmaceutics Database

IV Compatibility of Ketamine hydrochloride with:

	Admixture	Syringe	Y-Site Administration	For Dilution
Acetaminophen	C	ND	ND	ND
Acyclovir sodium	ND	I	I	ND
Albumin Human	ND	C	C	ND
Amikacin sulfate	ND	C	C	ND
Aminophylline	ND			ND
Amiodarone hydrochloride	ND	C	C	ND
Ampicillin sodium	ND	I	I	ND
Arsenic trioxide	ND	ND	C	ND
Atropine sulfate	ND	C	C	ND
Bupivacaine hydrochloride	ND	C	ND	ND
Caffeine citrate	ND	C	C	ND
Calcium gluconate	ND	C	C	ND
Cefazolin sodium	ND	C	C	ND
Cefepime hydrochloride	ND	ND	C	ND
	Admixture	Syringe	Y-Site Administration	For Dilution

Cefotaxime	ND	C	C	ND
Ceftazidime	ND	C	C	ND
Cefuroxime	ND	C	C	ND
Chlorpromazine hydrochloride	ND	C	C	ND
Clindamycin phosphate	ND	C	C	ND
Clonidine hydrochloride	C	C	C	ND
Cloxacillin sodium	ND	C	C	ND
Cyclosporine	ND	U	U	ND
D5W-Dextrose 5%	ND	ND	ND	C
Dexamethasone sodium phosphate	ND	U	U	ND
Diazepam	C	ND	ND	ND
Digoxin	ND	C	C	ND
Dimenhydrinate	ND	C	C	ND
Diphenhydramine hydrochloride	ND	C	C	ND
Dobutamine hydrochloride	ND	C	C	ND
	Admixture	Syringe	Y-Site Administration	For Dilution
Dopamine hydrochloride	ND	C	C	ND
Doxapram hydrochloride	ND	I	ND	ND
Droperidol	C	ND	ND	ND
Epinephrine hydrochloride	ND	C	C	ND
Fentanyl citrate	C	C	ND	ND
Furosemide	ND	I	I	ND
Gentamicin sulfate	ND	C	C	ND
Haloperidol lactate	ND	ND	C	ND
Heparin sodium	ND	I	I	ND
Hydrocortisone sodium succinate	ND	C	C	ND
Hydromorphone hydrochloride	C	C	ND	ND
Hydroxybutyric acid	ND	ND	I	ND
Insulin, regular	ND	I	I	ND
Ketoprofen	C	ND	ND	ND
Lidocaine hydrochloride	ND	C	ND	ND
	Admixture	Syringe	Y-Site Administration	For Dilution
Lorazepam	ND	U	U	ND
Lormetazepam	ND	ND	C	ND
Magnesium sulfate	ND	C	C	ND
Meperidine hydrochloride	ND	C	C	ND

Meropenem	ND	I	I	ND
Methylprednisolone sodium succinate	ND	C	U	ND
Metoclopramide hydrochloride	ND	C	C	ND
Metronidazole	ND	ND	C	ND
Midazolam hydrochloride	C	C	C	ND
Milrinone lactate	ND	C	C	ND
Morphine hydrochloride	ND	ND	C	ND
Morphine sulfate	C	C	ND	ND
Morphine tartrate	ND	C	ND	ND
Multiple vitamins injection	ND	C	C	ND
Naloxone hydrochloride	ND	C	C	ND
	Admixture	Syringe	Y-Site Administration	For Dilution
Nefopam hydrochloride	C	ND	ND	ND
Nitroglycerin	ND	U	U	ND
Normal saline- Sodium chloride 0.9%	ND	ND	ND	C
Oxycodone hydrochloride	ND	C	ND	ND
Oxytocin	ND	C	C	ND
Pancuronium bromide	ND	C	C	ND
Penicillin G potassium	ND	C	C	ND
Penicillin G sodium	ND	C	C	ND
Phenytoin sodium	ND	I	I	ND
Piperacillin sodium	ND	U	U	ND
Piperacillin sodium-tazobactam sodium	ND	C	C	ND
Piritramide	ND	ND	C	ND
Potassium chloride	ND	C	C	ND
Potassium phosphates	ND	I	I	ND
Promethazine hydrochloride	ND	C	C	ND
	Admixture	Syringe	Y-Site Administration	For Dilution
Propofol	ND	C	C	ND
Ranitidine hydrochloride	ND	C	C	ND
Ropivacaine hydrochloride	C	ND	ND	ND
Salbutamol	ND	U	U	ND
Sodium bicarbonate	ND	I	I	ND
Sterile water for injection	ND	ND	ND	C
Sufentanil citrate	C	ND	C	ND
Sulfamethoxazole-trimethoprim	ND	I	I	ND
Temocillin sodium	ND	ND	C	ND

Tetracaine hydrochloride	ND	C	ND	ND
Tiapride hydrochloride	ND	ND	C	ND
Ticarcillin disodium	ND	C	C	ND
Tobramycin sulfate	ND	C	C	ND
Vancomycin hydrochloride	ND	I	I	ND

How Supplied

Ketamine Hydrochloride Solution for injection

Ketalar 100mg/ml Solution for Injection (61570-0585) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc) (off market)

Ketalar 100mg/ml Solution for Injection (42023-0115) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc)

Ketalar 100mg/ml Solution for Injection (61570-0585) (Pfizer US Pharmaceuticals formerly Monarch Pharmaceuticals Inc) (off market)

Ketalar 10mg/ml Solution for Injection (61570-0581) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc) (off market)

Ketalar 10mg/ml Solution for Injection (42023-0113) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc)

Ketalar 10mg/ml Solution for Injection (61570-0581) (Pfizer US Pharmaceuticals formerly Monarch Pharmaceuticals Inc) (off market)

Ketalar 50mg/ml Solution for Injection (61570-0582) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc) (off market)

Ketalar 50mg/ml Solution for Injection (42023-0114) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc)

Ketalar 50mg/ml Solution for Injection (61570-0582) (Pfizer US Pharmaceuticals formerly Monarch Pharmaceuticals Inc) (off market)

Ketamine Hydrochloride 100mg/ml Solution for Injection (10139-0056) (GeneraMedix Pharmaceuticals Inc.)

Ketamine Hydrochloride 100mg/ml Solution for Injection (00409-2051) (Hospira Worldwide Inc.)

Ketamine Hydrochloride 100mg/ml Solution for Injection (00074-2051) (Hospira Worldwide Inc.) (off market)

Ketamine Hydrochloride 100mg/ml Solution for Injection (67457-0108) (Mylan Institutional LLC formerly BionichePharma Inc.)

Ketamine Hydrochloride 10mg/ml Solution for Injection (67457-0181) (Mylan Institutional LLC formerly BionichePharma Inc.)

Ketamine Hydrochloride 200mg/20ml Solution for Injection (42023-0137) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc) (off market)

Ketamine Hydrochloride 500mg/10ml Solution for Injection (42023-0138) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc) (off market)

Ketamine Hydrochloride 500mg/5ml Solution for Injection (42023-0139) (Par Sterile Products, LLC (formerly JHP Pharmaceuticals) a subsidiary of Par Pharmaceutical Inc)

Ketamine Hydrochloride 50mg/ml Solution for Injection (55390-0475) (Bedford Laboratories, A Hikma Company) (off market)

Ketamine Hydrochloride 50mg/ml Solution for Injection (00409-2053) (Hospira Worldwide Inc.)

Ketamine Hydrochloride 50mg/ml Solution for Injection (00074-2053) (Hospira Worldwide Inc.) (off market)

Ketamine Hydrochloride 50mg/ml Solution for Injection (67457-0001) (Mylan Institutional LLC formerly BionichePharma Inc.)

Monitoring Parameters

- laboratory monitoring not necessary

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Published on *Cath Lab Digest* (http://www.cathlabdigest.com)

Conscious Sedation in the Cath Lab: Should we use what GI uses?

[1]

[2]

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Issue Number: Volume 17 - Issue 1 - January, 2009 [4]

How much is enough conscious sedation (CS) for a cardiac catheterization procedure? Each lab likely has its own regimen. In our lab, most of our patients receive preprocedural oral valium (5mg) and Benadryl (25mg). In the lab, before the vascular access, we give versed (1-2mg) and fentanyl (25-50mcg) intravenously. Our patient is generally comfortable, sleepy, but can be aroused and conversant enough to tell us about pain or other problems. If the patient is agitated or highly anxious, we give additional doses of versed and fentanyl.

However, for GI and other procedures, the doses of CS drugs are much greater and with greater residual effects. Forgive my "shaggy dog" story, but I learned this after my own GI procedure and reading the report in which the GI doctor gave me 6mg intravenous versed and 150mcg fentanyl. This seemed to me, a simple cardiologist, like a lot of sedation and it certainly explained my unusual morning after the procedure. After an hour in the recovery area, I was wheeled out to our waiting car. Still "under the influence" (of conscious sedation) unbeknownst to me, I asked my wife if I could drive home. After she stopped laughing, she said "no," but I could go to breakfast with her. At breakfast, I focused intensely on my identification wrist band and since I had no desire to be labeled as "recently hospitalized," I pulled and tugged the band to rip it off, succeeding with a jerk, and knocking the coffee cup in front of me into the air and all over my wife. Her jump and scream snapped me back to reality.

I sat stunned. All I could do was say (like an oaf), "Wow, you've got great reflexes." She said to me, "You're still zonked. Finish your eggs and let's get you home." I didn't think I was so affected for so long after the procedure. I slept the rest of the day. I now better understand and in a very personal way why labs insist on having someone accompany the patient to any procedure in which conscious sedation is used and having them drive the patient home.

After considering how much medication the GI team used, I wanted to see what the variance of the cath lab conscious sedation practice was. I polled some of my friends in cath labs around the country and the world. My survey involved 30 cath lab doctors, two in Europe. Needless to say, they were entertained by my index event. Their regimens are summarized in Table 1.

The survey also indicated several things: 1) Most labs give nearly the same versed/fentanyl doses; 2) It is highly variable if valium and Benadryl are routinely given. Few reported this practice; 3) Morphine (2mg) was occasionally used in only one lab; 4) Other medications are infrequently required, e.g., Zofran for nausea (4mg IV); 5) Two labs used no conscious sedation (Switzerland and St. Louis2).

The definition of CS is worth remembering. CS is a minimally depressed level of consciousness that retains the patient's ability to maintain a patent airway independently and continuously, and respond appropriately to physical stimulation and verbal commands. Conscious sedation should be distinguished from two other levels of consciousness: deep sedation and general anesthesia. Deep sedation is a controlled state of depressed consciousness or unconsciousness from which the patient is not easily aroused, accompanied by a partial or complete loss of protective reflexes, including the ability to maintain a patent airway independently and respond purposefully to physical stimulation or verbal command. Patients must be suitable to receive CS according to the five classes of patients categorized by the American Society of Anesthesia guidelines:

Class I: Normally healthy
Class II: Patient with mild systemic disease (e.g., hypertension)
Class III: Patient with severe systemic disease (e.g., congestive heart failure), non-decompensated
Class IV: Patient with severe systemic disease, decompensated
Class V: Moribund patient, survival unlikely

Procedural sedation is appropriate for patients in Classes I, II and III. Patients in classes IV and higher are better suited for general anesthesia. There are several contraindications to CS, which include:

1. Recent (2. Physical class IV or greater
3. Lack of support staff or monitoring equipment
4. Lack of experience/credentialing on part of clinician

Common drugs used for CS are listed in Table 2.

The most serious problem of respiratory depression with oxygen desaturation may require reversal of sedation. Naloxone is a competitive antagonist of the opioid receptors; it is used for reversal of narcotic analgesics. Use 0.001 mg/kg IM/IV titrated to effect. Be aware that the duration of naloxone is less than the duration of action for most opiates. Be prepared to re-bolus the naloxone, or use a naloxone drip at .01-.05 mg/min.

Flumazenil is a pure benzodiazepine antagonist and can be used for reversal of benzodiazepine sedation. Like naloxone, it has a shorter duration of action than the benzodiazepine agents it reverses. Prepare to re-bolus with flumazenil, or run a flumazenil drip at 0.1 mg/min. Use 0.2 mg IV every 2-5 minutes titrated to effect, or up to 2-3 mg in total if needed.

It should be clear why there is such a difference between GI and cardiac cath lab conscious sedation. When you get a GI procedure, you don't want to feel anything and you don't have to do or say anything. When you get a cardiac cath, you still don't want to feel anything but you may have to cough, talk or hold your breath. You may be asked if you are having any discomfort or chest pain or to move your toes (CVA?). Cardiac cath operators need patient feedback at times, unlike the GI doctors who need you to relax, deeply. It is reassuring that the margin of safety with higher doses of commonly conscious sedation medications used in cardiac catheterization is so large. As one who has first-hand experience, the best part of CS for any of these procedures is the amnesia and knowing the procedure is over when you see the nurses' and your wife's smiling faces wheeling you out to the car.

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CASE STUDY: COMBATIVE CARDIAC PATIENT

What do you do when a patient regains consciousness during mechanical CPR?

By Oren Wacht, PhD, EMT-P, Refael Huri, EMT-P, & Refael Strugo, MD

Responsiveness during cardiac arrest presents a real challenge for EMS providers. For some patients, the use of a compression device during CPR can produce enough cardiac output to increase level of consciousness.

This case review presents a patient in cardiac arrest who received immediate bystander CPR and could not be intubated or given IV drugs by paramedics because of his level of consciousness while a compression device was active. The patient received ALS resuscitation, gained ROSC in the prehospital setting and was released from the hospital without any neurological damage. We suggest a treatment option for patients in this unique situation.

Introduction

The quality of basic life support (BLS) is critical to the outcomes of patients in OHCA.[1] One of the most important elements of BLS is delivering high-quality chest compressions during CPR.[2]

Although the literature is not conclusive about the benefits of mechanical compression devices, many EMS agencies have adopted them.[3] The reasons for their adoption are varied and include fatigue of the EMS team while delivering compressions, teams composed of only two providers, and maintenance of high-quality CPR during

transport for patients who are quality candidates for advanced hospital procedures such as PTCA (percutaneous transluminal coronary angioplasty), E-ECLS (emergency extracorporeal life support) and potential organ donation.[4,7]

One consideration with mechanical compression devices is the potential to produce enough cardiac output for patients to regain responsiveness or even feel pain.[8] This case review describes a patient in cardiac arrest who was combative during mechanical compressions and the resulting dilemma regarding the use of sedation or analgesia. To date there are no published guidelines for pain management during chest compressions.

Case Report: Witnessed Arrest With Bystander CPR

A 57-year-old physician in a large metropolitan area in Israel collapsed suddenly. An ambulance was dispatched after a call to EMS (see *Table 1*). Two bystander physicians began immediate compression-only CPR, and the patient regained consciousness.

After a few seconds the patient collapsed again, and compression-only CPR was restarted. The mobile intensive care unit (MICU) dispatched to the scene included four team members: two paramedics, one EMT and a paramedic student. It arrived in less than 10 minutes after the EMS call. The physicians on scene continued delivering compressions until EMS arrived.

EMS found the patient gasping, and immediately one of the team members replaced the physician performing compressions, while another ventilated the patient with a bag-valve device connected to oxygen. The patient was found to be in ventricular fibrillation (VF). A 200-joule biphasic shock was delivered, and BLS continued with minimal interruption while a mechanical compression device (LUCAS 2) was attached to the patient. No medical history for this patient was available on scene.

At this time the patient, still in VF, began moving his hands toward the compression device and grabbed it. While the compressions were paused for ventilation, the patient became flaccid again until the device delivered another compression. The

TABLE 1: TIMETABLE OF EVENTS

17:57 Call to EMS
17:58 Ambulance leaves station
18:06 Ambulance arrives on scene
18:39 Ambulance leaves scene for hospital
18:45 Ambulance arrives at hospital

team decided not to intubate the patient, since his level of consciousness indicated it would not be possible without sedation, and concentrated on the quality of BLS delivery.

Efforts to gain vascular access became difficult since the patient had folded his hands and would not allow the paramedics to straighten them. BLS continued without interruption for a total of three rounds of two minutes each, with a total of three 200-joule shocks every two minutes. Without vascular access, no epinephrine was administered, and the airway was managed with an oropharyngeal airway (tolerated for most of the time) and the bag-valve device. At this time the paramedics did not know if sedation by administration of midazolam, etomidate or ketamine was possible for a patient in cardiac arrest, since this situation was never before discussed or encountered. Eventually the paramedics obtained vascular access via an intraosseous device to the left tibia and continued CPR. The patient maintained purposeful movement.

After three shocks and six minutes of CPR, the patient achieved ROSC, and his heart rhythm changed to ventricular tachycardia. Two synchronized shocks were delivered until the rhythm changed to sinus tachycardia with a corresponding pulse. At this time the patient became restless, and the crew administered IO midazolam. The patient was hemodynamically stable, and the electrocardiogram showed no signs of ischemia, ST elevation or other changes suggesting a reason for the cardiac arrest. The nearest hospital's intensive cardiac care unit advised transport to the ER. On the short ride to the hospital, the patient woke up and was fully aware of what had happened.

AT THIS TIME THE PATIENT, STILL IN VF, BEGAN MOVING HIS HANDS TOWARD THE COMPRESSION DEVICE AND GRABBED IT.

At the Hospital

The patient was admitted to the emergency department and transferred to the ICCU. His medical history included rheu-

matic heart disease, dyslipidemia, a history of smoking, and mechanical aortic and mitral valve replacement. In the last year the patient had experienced a few episodes of paroxysmal atrial fibrillation but was functioning normally, including doing daily exercise. After admission he had no episodes of chest pain, his ECG was normal, and he showed no electrolyte imbalances or QT changes.

The patient's heart echocardiogram demonstrated new heart failure—a significant change for the worse since his last echocardiogram in 2012, following a mitral valve replacement. The patient's cardiac coronary computed tomography angiogram (CTA) demonstrated hypertrophy of the septum and a nonrestrictive disease in his coronary arteries. Surgeons implanted a cardioverter-defibrillator, and the patient was released from the hospital with no neurological damage.

Discussion

While mechanical compression devices have become common in prehospital and hospital treatment, there are no current clinical guidelines for treating patients who regain consciousness during cardiac arrest. This phenomenon presents an interesting challenge for healthcare providers who are not used to treating responsive patients while performing CPR during such arrests. Some of the procedures that are usually performed (such as obtaining vascular access or intubation) require the patient to be unconscious, or at least to not resist treatment.

Currently, cardiac arrest drugs are limited to those intended to restore circulation (vasopressors, antiarrhythmics). The use of mechanical compression devices presents a new challenge that may indicate sedation of patients. Analgesic medications should be selected for minimal cardiovascular influence. Drugs that are currently being used in EMS systems for sedation, analgesia and anesthesia include:

- Short-acting benzodiazepines like midazolam and long-acting benzodiazepines like Assival;
- Ketamine—for sedation, analgesia and anesthesia;
- Etomidate—for general anesthesia and sedation;
- Opioids—morphine and fentanyl for analgesia and anesthesia.

We suggest using fentanyl or ketamine for patients who gain some level of consciousness while a mechanical compression device is working.

Fentanyl is a synthetic opioid that is becoming common in EMS systems, as it has sedative and analgesic but minimal cardiovascular effects. While today in some systems it's administered intranasally for safety reasons, drugs in cardiac arrest should be administered

through an intravenous or intraosseous catheter according to current guidelines and since intranasal absorption is probably diminished in cardiac arrest. Ketamine is also a common drug that can provide analgesia and sedation with minimal cardiovascular effects and be used via the IV or IO route.

As mechanical compression devices gain popularity in EMS systems, research in this area should be conducted so clear guidelines can be published and practiced in hospitals and, especially, in prehospital settings.

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Ketamine *(Lexi-Drugs)*

Drug Shortages One or more forms of this drug may be in short supply or unavailable. Refer to the following for additional information:

SCCM: Alternative Medications for Procedural Sedation (Adults >18 Years of Age)

Pronunciation (KEET a meen)

Brand Names: Canada Ketalar; Ketamine Hydrochloride Injection, USP

Pharmacologic Category General Anesthetic

Dosing: Adult May be used in combination with anticholinergic agents to decrease hypersalivation. **Note:** Titrate dose for desired effect.

Anesthesia:

Induction of anesthesia:

Manufacturer's labeling:

IM: 6.5 to 13 mg/kg

IV: 1 to 4.5 mg/kg

Alternate recommendations (off-label dosing): **Note:** lower doses may be used if adjuvant drugs (eg, midazolam) are administered (Miller 2010)

IM: 4 to 10 mg/kg (Green 1990; Miller 2010; White 1982)

IV: 0.5 to 2 mg/kg (Miller 2010; White 1982)

Maintenance of anesthesia: May administer supplemental doses of one-half to the full induction dose or a continuous infusion of 0.1 to 0.5 mg/minute (per manufacturer). **Note:** To maintain an adequate concentration of ketamine for maintenance of anesthesia, 1 to 2 mg/minute has been recommended (White 1982); doses in the range of 15 to 90 mcg/kg/minute (~1 to 6 mg/minute in a 70-kg patient) have also been suggested (Miller 2010). Concurrent use of nitrous oxide reduces ketamine requirements. Recent laboratory/clinical studies support the use of low-dose ketamine to improve postoperative analgesia/outcome (Adam 2005; Menigaux 2000).

Sedation/analgesia (off-label use):

Procedural (operative or nonoperative):

IM: 2 to 4 mg/kg (Miller 2010; White 1982); may follow with a continuous infusion if necessary. According to the American College of Emergency Physicians, the IV route is preferred; however if IV route unavailable, may administer 4 to 5 mg/kg as a single dose; may give a repeat dose (range: 2 to 4 mg/kg) if sedation inadequate after 5 to 10 minutes or if additional doses are required (ACEP [Green 2011]).

IV: 0.2 to 0.8 mg/kg (Miller 2010; Remérand 2009; White 1982; Zakine 2008); a maximum bolus dose of 50 mg was used in one study (Remérand 2009). May follow with a continuous infusion if necessary. According to the American College of Emergency Physicians, may administer 1 mg/kg over 30 to 60 seconds for procedural sedation. If initial sedation inadequate or repeated doses are necessary to accomplish a longer procedure, may administer incremental doses of 0.5 mg/kg every 5 to 15 minutes as needed (ACEP [Green 2011]).

Continuous IV infusion: 2 to 7 mcg/kg/minute (Hocking 2003; Remérand 2009; Zakine 2008)

Critically ill patients (as an adjunct to an opioid analgesic for non-neuropathic pain): IV Initial: 0.1 to 0.5 mg/kg bolus; followed by 0.83 to 6.7 mcg/kg/minute (equivalent to 0.05 to 0.4 **mg/kg/hour**) (SCCM [Barr 2013])

Dosing: Geriatric Refer to adult dosing.

Dosing: Pediatric

Anesthesia: Adolescents ≥16 years: Refer to adult dosing.

Sedation/analgesia (off-label use): Adolescents ≥16 years: Refer to adult dosing.

Sedation (procedural) (off-label use): Children: American College of Emergency Physicians recommendations:

IM: 4 to 5 mg/kg as a single dose; may give a repeat dose (range: 2 to 4 mg/kg) if sedation inadequate after 5 to 10 minutes or if additional doses are required (ACEP [Green 2011]).

IV: 1.5 to 2 mg/kg over 30 to 60 seconds. If initial sedation inadequate or repeated doses are necessary to accomplish a longer procedure, may administer incremental doses of 0.5 to 1 mg/kg every 5 to 15 minutes as needed (ACEP [Green 2011]).

Dosing: Renal Impairment There are no dosage adjustments provided in the manufacturer's labeling.

Dosing: Hepatic Impairment There are no dosage adjustments provided in the manufacturer's labeling.

Use: Labeled Indications Induction and maintenance of general anesthesia

Use: Off-Label

▼ **Complex regional pain syndrome** Level of Evidence [B, G]

Data from controlled and noncontrolled trials suggest beneficial effects of subanesthetic ketamine infusions in the management of CRPS, particularly in patients diagnosed with CRPS-1. However, the dosage range varies considerably and an optimal dosage has not been established. In addition, inpatient administration or close patient monitoring in an outpatient clinic setting is recommended due to a high incidence of psychomimetic reactions (eg, hallucinations). Monitoring for hepatotoxicity is warranted. Larger, controlled trials are needed. Access Full Off-Label Monograph

▼ **Additional Off-Label Uses**

Analgesia; Sedation (procedural)

Level of Evidence Definitions

► **Level of Evidence Scale**

A - Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (eg, results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit.

B - Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.

C - Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain.

G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

Clinical Practice Guidelines

Critical Care:

"Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit," January 2013

Administration: IV According to the manufacturer, may administer bolus/induction doses over 1 minute or at a rate of 0.5 mg/kg/minute; more rapid administration may result in respiratory depression and enhanced pressor response. Some experts suggest administration over 2 to 3 minutes (Miller 2010).

Administration: Oral Mix the appropriate dose (using the 100 mg/mL injectable solution) in cola or other beverage; administer immediately after preparation.

Storage/Stability Store at 20°C to 25°C (68°F to 77°F). Protect from light.

Preparation for Administration The 50 mg/mL and 100 mg/mL vials may be further diluted in D_5W or NS to prepare a maintenance infusion with a final concentration of 1 mg/mL (or 2 mg/mL in patients with fluid restrictions). The 10 mg/mL vials are not recommended to be further diluted. Do not mix with barbiturates or diazepam (precipitation may occur). **Note:** The 100 mg/mL concentration should not be administered IV unless properly diluted with an equal volume of SWFI, NS, or D_5W.

Compatibility Stable in D_5W, NS.

Y-site administration: Compatible: Cefepime, ceftazidime, propofol.

Compatibility in syringe: Compatible: Bupivacaine, bupivacaine with fentanyl, clonidine, clonidine with tetracaine, dexamethasone sodium phosphate, fentanyl, lidocaine, lidocaine with morphine, meperidine, midazolam. **Incompatible:** Diazepam, doxapram. **Variable (consult detailed reference):** Morphine.

Medication Patient Education with HCAHPS Considerations

- Discuss specific use of drug and side effects with patient as it relates to treatment. (HCAHPS: During this hospital stay, were you given any medicine that you had not taken before? Before giving you any new medicine, how often did hospital staff tell you what the medicine was for? How often did hospital staff describe possible side effects in a way you could understand?)
- Patient may experience fatigue, lack of appetite, or nausea. Have patient report immediately to prescriber severe dizziness, syncope, dyspnea, tachycardia, bradycardia, arrhythmia, considerable headache, illogical thinking, hallucinations, behavioral changes, muscle rigidity, vision changes, involuntary eye movements, dysuria, or significant injection site irritation (HCAHPS).
- Educate patient about signs of a significant reaction (eg, wheezing; chest tightness; fever; itching; bad cough; blue skin color; seizures; or swelling of face, lips, tongue, or throat). **Note:** This is not a comprehensive list of all side effects. Patient should consult prescriber for additional questions.

Intended Use and Disclaimer: Should not be printed and given to patients. This information is intended to serve as a concise initial reference for healthcare professionals to use when discussing medications with a patient. You must ultimately rely on your own discretion, experience and judgment in diagnosing, treating and advising patients.

Medication Safety Issues

- **Sound-alike/look-alike issues:**

  Ketalar may be confused with Kenalog, ketorolac

- **High alert medication:**

  The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Contraindications

Hypersensitivity to ketamine or any component of the formulation; conditions in which an increase in blood pressure would be hazardous

Additional absolute contraindications according to the American College of Emergency Physicians (ACEP [Green 2011]): Infants <3 months of age; known or suspected schizophrenia (even if currently stable or controlled with medications)

Warnings/Precautions

Concerns related to adverse effects:

- Airway complications: When used for procedural sedation for major procedures involving the posterior pharynx (eg, endoscopy) or when used for patients with an active pulmonary infection or disease (including upper respiratory disease or asthma), the

use of ketamine increases the risk of laryngospasm. Patients with a history of airway instability, tracheal surgery, or tracheal stenosis may be at a higher risk of airway complications. The American College of Emergency Physicians considers these situations relative contraindications for the use of ketamine (ACEP [Green 2011]).

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). When used for outpatient surgery, the patient should be accompanied by a responsible adult.
- Dependence: May cause dependence (withdrawal symptoms on discontinuation) and tolerance with prolonged use.
- Emergence reactions: Postanesthetic emergence reactions which can manifest as vivid dreams, hallucinations, and/or frank delirium occur; these reactions are less common in patients <15 years of age and >65 years and when given intramuscularly. Emergence reactions, confusion, or irrational behavior may occur up to 24 hours postoperatively and may be reduced by pretreatment with a benzodiazepine and the use of ketamine at the lower end of the dosing range. Avoid use in patients with schizophrenia; may exacerbate psychotic symptoms (Lahti 1995; Malhotra 1997). The American College of Emergency Physicians considers the use of ketamine in patients with known or suspected schizophrenia (even if currently stable or controlled with medications) an absolute contraindication (ACEP [Green 2011]).
- Increased intracranial pressure: The American College of Emergency Physicians considers the use of ketamine in patients with CNS masses, CNS abnormalities, or hydrocephalus a relative contraindication due to increased intracranial pressure produced by ketamine (ACEP [Green 2011]).
- Increased ocular pressure: Use with caution in patients with increased intraocular pressure and avoid use in patients with an open eye injury or other ophthalmologic disorder where an increase in intraocular pressure would prove to be detrimental; ketamine may further increase intraocular pressure (Nagdeve 2006; Cunningham 1986; Miller 2010). The American College of Emergency Physicians considers the use of ketamine in patients with glaucoma or acute globe injury a relative contraindication (ACEP [Green 2011]).
- Porphyria: The American College of Emergency Physicians considers the use of ketamine in patients with porphyria a relative contraindication due to enhanced sympathomimetic effect produced by ketamine (ACEP [Green 2011]).
- Respiratory depression: Rapid IV administration or overdose may cause respiratory depression or apnea. Resuscitative equipment should be available during use.
- Thyroid disorders: The American College of Emergency Physicians considers the use of ketamine in patients with a thyroid disorder or receiving a thyroid medication a relative contraindication due to enhanced sympathomimetic effect produced by ketamine (ACEP [Green 2011]).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, catecholamine depletion, hypertension, and tachycardia. Cardiac function should be continuously monitored in patients with increased blood pressure or cardiac decompensation. Ketamine increases blood pressure, heart rate, and cardiac output thereby increasing myocardial oxygen demand. The mechanism by which ketamine causes a sympathetic surge to stimulate the cardiovascular system has yet to be elucidated. The use of concurrent benzodiazepine, inhaled anesthetics, and propofol or administration of ketamine as a continuous infusion may reduce these cardiovascular effects (Miller 2010). The American College of Emergency Physicians recommends avoidance in patients who are already hypertensive and in older adults with risk factors for coronary artery disease (ACEP [Green 2011]).
- Cerebrospinal fluid (CSF) pressure elevation: Use with caution in patients with CSF pressure elevation; an increase in CSF pressure may be associated with use.
- Ethanol use: Use with caution in the chronic alcoholic or acutely alcohol-intoxicated.

Other warnings/precautions:

- Experienced physician: Should be administered under the supervision of a physician experienced in administering general anesthetics.

Pregnancy Considerations Adverse events have not been observed in animal reproduction studies. Ketamine crosses the

placenta and can be detected in fetal tissue. Ketamine produces dose dependent increases in uterine contractions; effects may vary by trimester. The plasma clearance of ketamine is reduced during pregnancy. Dose related neonatal depression and decreased APGAR scores have been reported with large doses administered at delivery (Ghoneim 1977; Little 1972; White 1982).

Breast-Feeding Considerations

It is not known if ketamine is excreted in breast milk.

Briggs' Drugs in Pregnancy & Lactation

- Ketamine

Adverse Reactions

Frequency not always defined.

Cardiovascular: Bradycardia, cardiac arrhythmia, hypotension, increased blood pressure, increased pulse

Central nervous system: Prolonged emergence from anesthesia (~12%; includes confusion, delirium, dreamlike state, excitement, hallucinations, irrational behavior, vivid imagery), drug dependence, hypertonia (tonic-clonic movements sometimes resembling seizures), increased cerebrospinal fluid pressure

Dermatologic: Erythema (transient), morbilliform rash (transient), rash at injection site

Endocrine & metabolic: Central diabetes insipidus (Hatab 2014)

Gastrointestinal: Anorexia, nausea, sialorrhea (Hatab 2014), vomiting

Genitourinary (adverse reactions can be severe in patients with a history of chronic ketamine use/abuse): Cystitis, irritable bladder, urethritis, urinary tract irritation

Hypersensitivity: Anaphylaxis

Local: Pain at injection site

Neuromuscular & skeletal: Laryngospasm

Ophthalmic: Diplopia, increased intraocular pressure, nystagmus

Respiratory: Airway obstruction, apnea, respiratory depression

Metabolism/Transport Effects

Substrate of CYP2B6 (major), CYP2C9 (major), CYP3A4 (major); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

Drug Interactions

Open Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). *Risk X: Avoid combination*

Brimonidine (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr in adults when used with other CNS depressants. *Risk D: Consider therapy modification*

Cannabis: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. **Exceptions:** Levocabastine (Nasal). *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C9 Inducers (Strong): May increase the metabolism of CYP2C9 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. *Risk D:*

Consider therapy modification

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates. *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabrafenib: May decrease the serum concentration of CYP2C9 Substrates. Management: Seek alternatives to the CYP2C9 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Doxylamine: May enhance the CNS depressant effect of CNS Depressants. Management: The manufacturer of Diclegis (doxylamine/pyridoxine), intended for use in pregnancy, specifically states that use with other CNS depressants is not recommended. *Risk C: Monitor therapy*

Dronabinol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (e.g., opioids, barbiturates) with concomitant use. *Risk D: Consider therapy modification*

Enzalutamide: May decrease the serum concentration of CYP2C9 Substrates. Management: Concurrent use of enzalutamide with CYP2C9 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP2C9 substrate should be performed with caution and close monitoring. *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Hydrocodone: CNS Depressants may enhance the CNS depressant effect of Hydrocodone. Management: Consider starting with a 20% to 30% lower hydrocodone dose when using together with any other CNS depressant. Dose reductions in the other CNS depressant may also be warranted. *Risk D: Consider therapy modification*

HydrOXYzine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Ivacaftor: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Kava Kava: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*

Luliconazole: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Lumacaftor: May decrease the serum concentration of CYP2C9 Substrates. Lumacaftor may increase the serum concentration of CYP2C9 Substrates. *Risk C: Monitor therapy*

Magnesium Sulfate: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Memantine: NMDA Receptor Antagonists may enhance the adverse/toxic effect of Memantine. *Risk C: Monitor therapy*

Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. *Risk D: Consider therapy modification*

Metyrosine: CNS Depressants may enhance the sedative effect of Metyrosine. *Risk C: Monitor therapy*

Mifepristone: May increase the serum concentration of CYP2C9 Substrates. Management: Use CYP2C9 substrates at the lowest recommended dose, and monitor closely for adverse effects, during and in the 2 weeks following mifepristone treatment. *Risk D: Consider therapy modification*

Mifepristone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. *Risk D: Consider therapy modification*

Minocycline: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Mirtazapine: CNS Depressants may enhance the CNS depressant effect of Mirtazapine. *Risk C: Monitor therapy*

Nabilone: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Netupitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. *Risk X: Avoid combination*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. *Risk X: Avoid combination*

Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. *Risk D: Consider therapy modification*

Pramipexole: CNS Depressants may enhance the sedative effect of Pramipexole. *Risk C: Monitor therapy*

Quazepam: May increase the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

ROPINIRole: CNS Depressants may enhance the sedative effect of ROPINIRole. *Risk C: Monitor therapy*

Rotigotine: CNS Depressants may enhance the sedative effect of Rotigotine. *Risk C: Monitor therapy*

Rufinamide: May enhance the adverse/toxic effect of CNS Depressants. Specifically, sleepiness and dizziness may be enhanced. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: CNS Depressants may enhance the adverse/toxic effect of Selective Serotonin Reuptake Inhibitors. Specifically, the risk of psychomotor impairment may be enhanced. *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. *Risk D: Consider therapy modification*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. *Risk D: Consider therapy modification*

Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Start tapentadol at a dose of one-third to one-half of the normal dose if being initiated in a patient who is taking another drug with CNS depressant effects. Monitor closely for evidence of excessive CNS depression. *Risk D: Consider therapy modification*

Tetrahydrocannabinol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. *Risk X: Avoid combination*

Thiopental: Ketamine may enhance the adverse/toxic effect of Thiopental. *Risk C: Monitor therapy*

Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem adult dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. *Risk D: Consider therapy modification*

Test Interactions May interfere with urine detection of phencyclidine (false-positive).

Genes of Interest

- Cytochrome P450, Family 2, Subfamily B, Polypeptide 6
- Cytochrome P450, Family 2, Subfamily C, Polypeptide 9
- Cytochrome P450, Family 3, Subfamily A, Polypeptide 4

Monitoring Parameters Heart rate, blood pressure, respiratory rate, transcutaneous O_2 saturation, emergence reactions; cardiac function should be continuously monitored in patients with increased blood pressure or cardiac decompensation

Nursing: Physical Assessment/Monitoring Monitor cardio/respiratory status and CNS status (when used for procedures monitor sedation score); cardiac monitor and blood pressure monitor required. Monitor for emergence reactions.

Controlled Substance C-III

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Injection:

Ketalar: 10 mg/mL (20 mL); 50 mg/mL (10 mL); 100 mg/mL (5 mL)

Generic: 10 mg/mL (20 mL); 50 mg/mL (10 mL); 100 mg/mL (5 mL, 10 mL)

Anatomic Therapeutic Chemical (ATC) Classification

- N01AX03

Generic Available (US) Yes

Pricing: US

Solution (Ketalar Injection)

10 mg/mL (20 mL): $21.60

50 mg/mL (10 mL): $6.36

100 mg/mL (5 mL): $11.85

Solution (Ketamine HCl Injection)

10 mg/mL (20 mL): $17.78

50 mg/mL (10 mL): $4.28

100 mg/mL (5 mL): $9.78

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

Mechanism of Action Produces a cataleptic-like state in which the patient is dissociated from the surrounding environment by direct action on the cortex and limbic system. Ketamine is a noncompetitive NMDA receptor antagonist that blocks glutamate. Low (subanesthetic) doses produce analgesia, and modulate central sensitization, hyperalgesia and opioid tolerance. Reduces polysynaptic spinal reflexes.

Pharmacodynamics/Kinetics

Onset of action:

IV: Anesthetic effect: 30 seconds

IM: Anesthetic effect: 3-4 minutes

Duration: Anesthetic effect: IV: 5-10 minutes; IM: 12-25 minutes

Distribution: V_d: 3 L/kg

Metabolism: Hepatic via hydroxylation and N-demethylation; the metabolite norketamine is 33% as potent as parent compound; greater conversion to norketamine occurs after oral administration as compared to parenteral administration

Bioavailability: Oral: 16%; Intranasal: 50%

Half-life elimination: Alpha: 10-15 minutes; Beta: 2.5 hours

Excretion: Primarily urine

Local Anesthetic/Vasoconstrictor Precautions

No information available to require special precautions

Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Increased salivation.

Effects on Bleeding

No information available to require special precautions

Related Information

- Acute Postoperative Pain
- Anesthesia Considerations for Neurosurgery
- Anesthesia for Obstetric Patients in Nonobstetric Surgery
- Anesthetic Agents
- Chemotherapy-Induced Peripheral Neuropathy
- Chronic Pain Management (Cancer)
- Dosing Considerations for the Critically Ill Patient With Morbid Obesity
- Inhalational Anesthetics
- Palliative Care Medicine (Cancer)

Pharmacotherapy Pearls

May produce emergence psychosis including auditory and visual hallucinations, restlessness, disorientation, vivid dreams, and irrational behavior in ~12% of patients; pretreatment with a benzodiazepine reduces incidence of psychosis by >50%. Spontaneous involuntary movements, nystagmus, hypertonus, and vocalizations are also common.

The analgesia outlasts the general anesthetic component. Bronchodilation is beneficial in asthmatic or COPD patients. Laryngeal reflexes may remain intact or may be obtunded. The direct myocardial depressant action of ketamine can be seen in stressed, catecholamine-deficient patients. Ketamine increases cerebral metabolism and cerebral blood flow while producing a noncompetitive block of the glutaminergic postsynaptic NMDA receptor. It lowers seizure threshold and stimulates salivary secretions (atropine/scopolamine treatment is recommended).

Index Terms

Ketamine Hydrochloride

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International Brand Names Aneket (ET); Anesject (ID); Brevinaze (ZA); Calypsol (AE, BB, BG, BH, BM, BS, BZ, CY, CZ, EG, GY, HN, HU, IQ, IR, JM, JO, KW, LB, LY, OM, PK, PL, PR, QA, RO, RU, SA, SR, SY, TT, VN, YE); Cost (AR, BR); Etamine (PH); Ivanes (ID); Kanox (MY); Katalar (QA); Keiran (VE); Ketalar (AE, AU, BB, BE, BH, BM, BS, BZ, CH, CY, DK, EE, EG, ES, FI, FR, GB, GR, GY, HK, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KW, LB, LU, LY, MT, MY, NO, NZ, OM, PE, PT, QA, SA, SE, SK, SR, SY, TR, TT, TW, UY, YE); Ketalin (MX); Ketam (ET); Ketamax (PH); Ketamin-S (+) (PY); Ketanest (AT, HR, NL, PL); Ketashort (CO); Ketava (MY); Ketazol (PH); Ketmin (IN); Ketolar (ES); Ketomin (KR); Narkamon (DE, PL); Tekam (AE, BH, CY, EG, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Velonarcon (PL)

Resuscitation 86 (2015) 44–48

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review article

Return of consciousness during ongoing cardiopulmonary resuscitation: A systematic review☆

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ARTICLE INFO

Article history:
Received 8 August 2014
Received in revised form 8 October 2014
Accepted 28 October 2014

Keywords:
Cardiopulmonary resuscitation
Consciousness
Awareness
Emergency Care, Prehospital
Incidence
Outcome

ABSTRACT

Objectives: Cardio-pulmonary resuscitation (CPR) may generate sufficient cerebral perfusion pressure to make the patient conscious. The incidence and management of this phenomenon are not well described. This systematic review aims to identifying cases where CPR-induced consciousness is mentioned in the literature and explore its management options.

Methods: The databases Medline, PubMed, EMBASE, Cinahl and the Cochrane Library were searched from their commencement to the 8th July 2014. We also searched Google (scholar) for grey literature. We combined MeSH terms and text words for consciousness and CPR, and included studies of all types.

Results: The search yielded 1997 unique records, of which 50 abstracts were reviewed. Nine reports, describing 10 patients, were relevant. Six of the patients had CPR performed by mechanical devices, three of these patients were sedated. Four patients arrested in the out-of-hospital setting and six arrested in hospital. There were four survivors. Varying levels of consciousness were described in all reports, including purposeful arm movements, verbal communication, and resuscitation interference. Management strategies directed at consciousness were offered to six patients and included both physical and chemical restraints.

Conclusion: CPR-induced consciousness was infrequently reported in the medical literature, and varied in management. Given the increasing use of mechanical CPR, guidelines to identify and manage consciousness during CPR are required.

1. Background

Cardio-pulmonary resuscitation (CPR) facilitates blood flow throughout the body.[1] Good quality cardiac compressions reportedly provide 30% of normal pre-arrest cardiac output.[2] The latest resuscitation guideline update focuses on improved quality of CPR with emphasis on depth and rate of chest compressions with minimal interruptions thereby improving cerebral perfusion pressure (CPP).[3] CPP correlates closely with brain oxygenation during CPR.[4] One potential consequence of good quality resuscitation is therefore CPR-induced consciousness. The incidence of CPR-induced consciousness remains unknown.

Martens and Mullie[5] asked two decades ago whether sedation during CPR required a treatment guideline. Currently there are no recommendations by the International Liaison Committee on Resuscitation (ILCOR) for either pharmaceutical or physical management of CPR-induced consciousness.[3] Avenues for the management strategies are unclear.

Among patients with CA, we aimed to identify cases of CPR-induced consciousness, perceivable by the rescuer, in the literature and management strategies.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.10.017.

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http://dx.doi.org/10.1016/j.resuscitation.2014.10.017
0300-9572/

2. Methods

2.1. Search strategy

This systematic review searched English and non-English literature according to PRISMA guidelines.[6] A combination of the subject headings (/) and key words (".") was used in the following way: (*Consciousness/or Awareness/or Perception/or Pain perception/or Movement/or Wakefulness/or "combative" or "alert" or "awake") AND (CPR/or "cardiopulmonary resuscitation" or "cardiopulmonary resuscitations" or "resuscitation cardiopulmonary" or "heart resuscitation" or "cardio pulmonary resuscitation" or "cardiac resuscitation"*).

2.2. Eligibility criteria

Patients: patients of any age receiving CPR within any arrest setting (e.g. out-of-hospital, in-hospital, ICU).

Exposure: CPR-induced consciousness detectable by the rescuer
Comparison: Unconscious in the same study
Outcome: Any reported outcome
Study types: All study types

Articles were excluded if they only reported on consciousness before or after CPR. Further, we excluded reports that described bispectral index (BIS) monitoring as the only measure of awareness, cough-CPR or subjective near-death experiences.

2.3. Information sources

We searched for articles from five databases (Medline, PubMed, EMBASE, Cinahl and The Cochrane Library), extending from the databases' commencement to the 8th of July 2014. Google and Google scholar were used for grey literature searching.

2.4. Study selection

Following the search, duplicates were removed and titles subsequently appraised for eligibility independently by two authors (AO and MS). The abstracts of the selected titles were read, and full-texts were sought for articles meeting the inclusion criteria. Consensus resolved any disagreements concerning inclusion decisions. Reference lists of relevant articles were checked for additional studies.

2.5. Data extraction

From the included papers we extracted demographic data, arrest setting, aetiology and rhythm, level of consciousness, CPR method and time, management and reported outcomes.

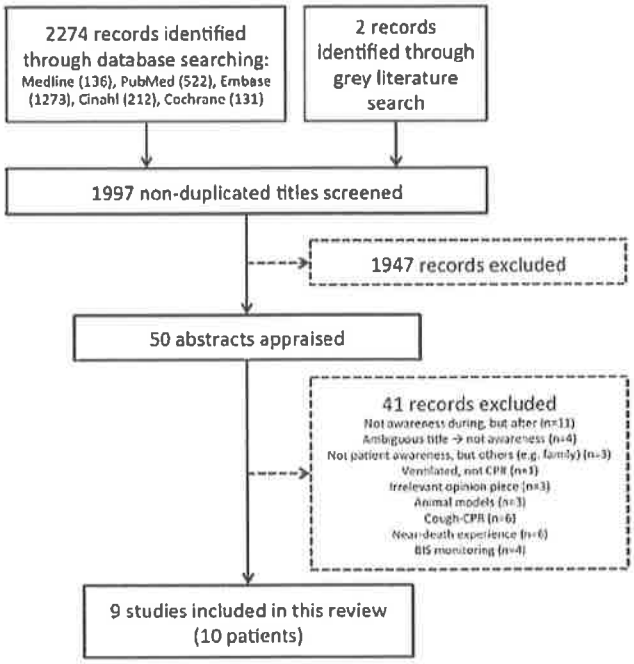

Fig. 1. CPR-induced consciousness PRISMA flow chart.

3. Results

The initial search yielded 2274 records, of which 1997 were unique. Fifty titles met the inclusion criteria; of which 41 were excluded as per protocol (Fig. 1). The nine included reports described 10 patients with a median age of 57 (IQR: 56–60).[7–15] Six of these reports originated in the USA, two from France, one from Canada and one from Taiwan. Six out of 10 arrests occurred in hospital (Table 1). In five of the six in-hospital reports, CPR was commenced immediately after cardiac arrest. In the report by Lewinter et al. the patient received an immediate 300 J countershock before mechanical compressions were initiated. In the four cases of out-of-hospital cardiac arrest, one patient had CPR commenced within 1 min, while the remaining cases did not report the timing to CPR.

The level of consciousness included purposeful arm movements in all cases. Additionally, the reports ranged from describing agonal breaths, eye opening and localising painful stimuli. Communication with the rescuer, both verbally and non-verbally were detailed, with a few patients understanding and adhering to the instructions received. In contrast, agitation and attempts to push the rescuer away were also noted. In one case the patient indicated a wish to cease resuscitation. No study reported the coma score using the Glasgow Coma Scale. The timing of consciousness, when

Table 1
Study quality.

Study author	Country	Patient(s), age, gender	Setting	Arrest rhythm	Aetiology of arrest
Frédéric et al.[8]	France	57 yo male & 58 yo male	Pre-hospital	NR	NR
Tobin and Mihm[12]	USA	62 yo male	In-hospital	PEA	Heart failure
Yu et al.[13]	Taiwan	27 yo female	ICU	VT	Myocarditis
Bihari and Rajajee[7]	USA	57 yo male	ICU	Asystole	Renal failure
Quinn et al.[11]	Canada	57 yo male	ED	PEA	AMI
Lewinter et al.[9]	USA	60 yo female	ED	VT	AMI
McDonald[10]	USA	Mid-forties male	ED	VF	AMI
Fauber[14]	USA	56 yo male	Pre-hospital	VF	NR
Heightman and Greb[15]	USA	61 yo male	Pre-hospital	VF	Arrhythmia

NR = not reported; yo = year-old; ICU = intensive care unit; ED = emergency department; VT = ventricular tachycardia; VF = ventricular fibrillation; PEA = pulseless electrical activity; AMI = acute myocardial infarction.

reported, occurred mainly at the beginning of the arrest. In cases using mechanical CPR devices, consciousness occurred within a few compressions, and disappeared with brief CPR pauses. In two cases,[7,13] the patient was in and out of consciousness for the first 2 h.

Six patients had CPR performed by mechanical devices, three of these patients were sedated after consciousness was perceived, and three others had no specific management towards consciousness (Table 2). One of the four patients who received standard CPR was sedated. Other actions for the management of consciousness included physical restraint ($n = 2$), and instructions to the patient to refrain from reaching for the endotracheal tube ($n = 1$).

The length of CPR was documented in six cases. The median resuscitation time was 141 min (IQR: 57–187 min). Extension of the resuscitation time due to the consciousness varied from normal care to transport to tertiary hospitals and extracorporeal membrane oxygenation (ECMO).

Five cases reported that the level of consciousness interfered with the resuscitation, including pushing and grabbing the rescuer, withdrawing from the compressions, and pulling on endotracheal tubes and mechanical devices. Seven cases noted an absence of consciousness during periods of pulse check. Three cases reported additional pulse checks and/or halting CPR, as it was believed that return of spontaneous circulation had occurred. Four of the 10 patients survived to hospital discharge, with one patient recalling the CPR, stating he "remember(ed) this guy on top of me, trying to hold me down, and I just couldn't get him off me".

4. Discussion

CPR-induced consciousness has been infrequently reported in the medical literature. Among reported cases, both the level and management of consciousness varied widely. Mechanical devices may be more commonly associated with consciousness during CPR than traditional chest compressions. A perceivable level of patient consciousness had variable influence on the decision to continue resuscitation efforts.

The cause for CPR-induced consciousness is unclear, but is likely the result of a combination of factors. Two cases[7,12] observed that a mean arterial pressure (MAP) exceeding 50 mmHg was sufficient to awaken their patients. No other reports included MAP readings. While manual chest compression rarely produce a MAP exceeding 40 mmHg,[3] reports of higher MAP readings without associated consciousness exist.[16] Individual factors, such as autoregulation,[17] ischaemic threshold,[18] and presence of co-morbidities[19] may also contribute to CPR-induced consciousness, as they may influence brain oxygenation. Furthermore, Bihari and Rajajee[7] speculated that early and skilled CPR by trained personnel (e.g. in-hospital witnessed arrest) are key factors leading to CPR-induced consciousness. Of the cases reviewed here, the majority occurred in hospital.

More than half (6 out of 10) of the reported cases occurred in the setting of mechanical CPR devices. While mechanical devices have not yet demonstrated improved survival rates compared with manual chest compressions, there is evidence supporting their role in improving the consistency of CPR while reducing interruptions,[20]

Table 2
Consciousness, management and outcome.

Study author, year	Description of consciousness	CPR	CPR time	Management of the consciousness	Survived to discharge
Frédéric et al.[8] (57yo male)	Arm movement upon request. Opened and closed eyes	Automated chest compressions	NR	NR	No
Frédéric et al.[8] (58yo male)	Spontaneous movements of both arms	Automated chest compressions	NR	Sedation (not specified)	No
Tobin and Mihm[12]	Reached for the ETT. Agonal breaths, wiggled toes, moved head, slightly open eyes. Gave "thumbs up" following explanation of the situation.	Manual	Approx. 120 min	The patient was told what was happening and that he had to refrain from pulling out the ETT	No
Yu et al.[13]	Alert and responsive with finger gestures	Manual	280 min	No	Yes
Bihari and Rajajee[7]	Brisk localisation of painful stimuli. Attempted to pull out the laryngoscope. Followed and responded to commands.	Manual	195 min	Physical restraint	No
Quinn et al.[11]	Purposeful movement. Agitation.	Active compression decompression device	36 min	Midazolam ($0.1\ mg\ kg^{-1}$) + succinylcholine ($1.5\ mg\ kg^{-1}$) Physical restraint	No
Lewinter et al.[9]	"Responsive"; "Maintained consciousness"	Thumper	162 min	Small doses" morphine sulfate + diazepam	No
McDonald[10]	Raised arms. Tried to push attending CPR-performer away	Manual	NR	Sedation (not specified)	Yes
Fauber[14]	Grabbed at paramedics. Questioned what they were doing.	ResQPOD & ResQpump	NR	NR	Yes
Heightman and Greb[15]	Moved limbs. Answered questions.	LUCAS Device	Approx. 20 min	NR	Yes

NR = not reported; ETT = endotracheal tube.

as well as improving CPP when compared to standard CPR.[21] There is a delay between changes to CPP and changes to brain oxygenation during CPR, which is approximately 1.7 min long.[4] Since manual CPR is paused briefly every second minute, while mechanical CPR can continue uninterrupted, it is likely that consciousness is a consequence of high quality uninterrupted compressions. If uninterrupted CPR becomes more common practice, either through increased use of mechanical CPR devices or improved manual CPR, CPR-induced consciousness may occur more frequently.

The conscious cardiac arrest patient may require specific management. The variation in consciousness described in the identified cases and the paucity of guidelines may explain the different treatment strategies deployed. Two common themes in the reviewed cases were CPR interruption for pulse checks and verification of the cardiac arrest, and patient interference with the resuscitation. Therefore, in situations of CPR-induced consciousness, interruptions to chest compressions are likely and require management. This might include education of the rescuers about the possibility of this presentation, and physical restraint and/or chemical restraint titrated to the patient's level of consciousness.

Four of the 10 patients described were sedated. Two cases did not describe the drug or dose used, one stated "small doses" of morphine and diazepam, while one case used 0.1 mg kg^{-1} of Midazolam. Although no universal ILCOR guideline exist,[3] local consensus-derived guidelines are emerging. A recently published Dutch guideline of pre-hospital CA[22] suggested that agitation and/or pain during (mechanical) chest compressions can be treated with 2 μg kg^{-1} of fentanyl IV (which can be titrated to 4 μg kg^{-1}), and 2.5 mg of Midazolam IV (which can be titrated to 5 mg). Other jurisdictions allow small doses of sedation to facilitate endotracheal intubation in the presence of a gag reflex.[23] These guidelines are not supported by high levels of evidence, but could potentially assist in delivering less interrupted CPR.

In the process of intubation, sometimes before or after CPR, a variety of sedative agents are commonly administered. Such agents include, but are not limited to, Propofol, Thiopentone, Ketamine, Etomidate and Remifentanyl. Common pre-hospital agents are Midazolam, Morphine and Fentanyl. Translating evidence for the use of such agents during CPR will require further studies. Selection of the most appropriate agent(s) and dose(s) will be influenced by the arrest setting (i.e. pre-hospital or in-hospital). Given the differences between these two settings in terms of level of training, jurisdictions and resources available, different treatment modalities are likely required. It is foreseeable that agents with minimal circulatory depression are optimal, as this concern is one of the main reasons clinicians may be reluctant to administer sedation during resuscitation.[7] Notwithstanding the relatively limited value of advanced life support medications on cardiac arrest outcome,[24,25] there would be concern that doses of sedation could impact on patient survival.

It is important to note that although agonal breaths may occur without return of spontaneous circulation,[3] the presence of respirations and/or pupillary reactivity could help to prolong resuscitation efforts.[26] The influence CPR-induced consciousness had on extending the resuscitation time in the reported cases varied. In the case by Yu et al.[13] despite 2 h of asystole, the presence of consciousness was instrumental in the decision to continue resuscitation efforts. In contrast, in the case by Quinn et al.[11] CPR efforts only lasted for 36 min, with the patient in asystole only during the last 14 min. In the case by Bihari and Rajajee,[7] absence of spontaneous breathing and presence of fixed pupils for 1 h was used to guide the decision to withdraw CPR.

The implication of CPR-induced consciousness on survival, and therefore the value of ongoing resuscitation, is not clear. In a case report of a cardiac arrest due to amniotic fluid embolus, positive bispectral index (BIS) levels (a measure of cerebral function and a surrogate for consciousness), was reportedly instrumental in deciding to continue resuscitation.[27] Although BIS monitoring does not appear to be associated with return of spontaneous circulation (ROSC) or survival,[28,29] other methods of cerebral oximetry measuring, such as non-invasive infrared spectroscopy may correlate with ROSC.[30,31] Awareness during CPR, as measured retrospectively in patients who are successfully resuscitated, have been described.[32] Although these recalls may provide insight into the nature of human consciousness,[33] they do not interfere with CPR and are currently not perceivable by rescuers.

Overall, the paucity of literature on CPR-induced consciousness limits evidence-based development of management guidelines, necessitating consensus-derived guidelines instead. This review does highlight some potential principles of such guidelines. Firstly, a clear definition CPR-induced consciousness signs are required, which arguably should extend beyond agonal breathing. Secondly, methods of sedation need to be effective and humane, while balanced against adverse effects. In the pre-hospital setting, where physiological monitoring may be more basic, such guidelines may necessarily be more conservative. Thirdly, with respect to the extension of CPR time, we echo the opinion of Yu et al.[13] and Frédéric et al.,[8] that the presence and availability of newer treatment alternatives, such as ECMO, should favour CPR extension. Where such options are available, prolonged CPR is being observed, often using mechanical devices, which are capable of delivering higher quality chest compressions over longer periods of time. As such, consciousness during CPR may become more of an emerging phenomenon as such practice becomes more widespread.

This review has limitations. We were interested in CPR-induced consciousness, but given the varied presentation we did not apply strict inclusion and exclusion criteria on the level of reported consciousness. We did not include cases of "awareness" as described in the anaesthetic literature, or near-death experiences since these presentations cannot be detected clinically and do not interfere with resuscitation. The included reports were case reviews, of which some did not undergo peer-review. The small number of reported cases raises the possibility of reporting bias, and limits its generalisability to cardiac arrest populations. The low number of reported cases also hinders evidence-based recommendations for guideline outlining management during consciousness during CPR.

5. Conclusion

CPR may induce consciousness but this is infrequently reported in the medical literature. Treatment strategies for CPR-induced consciousness varied widely, and included physical restraint, administration of a benzodiazepines and/or opiate, or no specific management. The incidence, implications and prognostic value of CPR-induced consciousness remains unknown. Increased awareness by rescuers of the presence of CPR-induced consciousness and development of consensus-based guidelines to treat this condition are required.

Conflict of interest statement

None of the authors have any financial or personal conflicts of interest that could inappropriately influence their work.

Funding

This systematic review did not receive any funding.

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Canadian Journal of Cardiology 30 (2014) 627–633

Clinical Research

Sedation, Analgesia, and Anaesthesia Variability in Laboratory-Based Cardiac Procedures: An International Survey

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ABSTRACT

Background: There is a paucity of data regarding the type of anaesthesia used and the perception toward anaesthesia among cardiologists, anaesthesiologists, and nurses. Our objective was to describe the use of sedation during nonsurgical cardiac procedures.

Methods: We designed a Web-based survey to assess anaesthesia practices during cardiac procedures. The survey was distributed to cardiologists, anaesthesiologists, and nurses through national societies and international investigator networks. The questions addressed the type of practice, type of anaesthesia used during procedures, and perceptions regarding anaesthesia.

Results: The survey was completed by 497 participants. Sedation during cardiac catheterization was used by 77/84 (92%) of cardiologists in North America, but only by 46/121 (38%) in other countries ($P < 0.0001$). Use of general anaesthesia for complex procedures such as transaortic valve replacement is also more common in North

RÉSUMÉ

Introduction : Il existe peu de données concernant le type d'anesthésie utilisée et le point de vue qu'ont les cardiologues, les anesthésiologistes et les infirmières et infirmiers sur l'anesthésie. Notre objectif était de décrire l'utilisation de la sédation durant les interventions cardiaques non chirurgicales.

Méthodes : Nous avons réalisé une enquête en ligne pour évaluer les pratiques d'anesthésie utilisées durant les interventions cardiaques. L'enquête a été distribuée aux cardiologues, aux anesthésiologistes et aux infirmières et infirmiers par les sociétés nationales et les réseaux internationaux de recherche. Les questions portaient sur le type de pratique, le type d'anesthésie utilisée durant les interventions et les points de vue sur l'anesthésie.

Résultats : L'enquête a été réalisée par 497 participants. La sédation durant le cathétérisme cardiaque était utilisée par 77/84 (92 %) cardiologues de l'Amérique du Nord, mais seulement par 46/121

Anaesthesia is commonly used during different laboratory-based cardiac procedures and usually includes local anaesthesia. The type of anaesthesia (eg, general, sedation, local anaesthesia, or a combination thereof) varies, and might depend on the type of procedure, the operator's experience, and patient request.

During diagnostic coronary angiography and percutaneous coronary intervention (PCI), 35% of patients treated with benzodiazepines and local anaesthesia complain about pain and discomfort, thus underscoring the need for analgesia and individualized anaesthesia care.[1] Routine use of sedation rather than local anaesthesia before sheath removal leads to a reduction in pain perceived by patients.[2] More complex percutaneous cardiac interventions such as transfemoral aortic valve implantation (TAVI) and percutaneous mitral valve repair require a team approach that includes an anaesthesiologist. Although these latter procedures are often performed with general anaesthesia, recent data suggest that some can be performed using sedation alone[3-5] and might be related to the level of experience with those complex procedures.[6]

Sedation is often provided by nonanaesthesia personnel because of lack of availability of the anaesthesia team or economic reasons[7,8] and in some centres, conscious sedation is provided by the cardiologist performing the procedure.[9] There is a paucity of data regarding who provides anaesthesia, and for which procedures, and the medications being used for conscious sedation.

Therefore, the aim of this study was to evaluate the type of anaesthesia used during various cardiac procedures, the type of medications administered, and the perception toward anaesthesia during these procedures among cardiologists, anaesthesiologists, and nurses.

Received for publication January 8, 2014. Accepted March 28, 2014.

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See page 633 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2014.03.034

America (92%) compared with other countries (76%; $P = 0.004$). Specific sedation-related training was provided to less than a third of nonanaesthesiologists. Although more than half of the nurses received training regarding procedural sedation, such training is provided to less than a quarter of the cardiologists. The lack of training was noted in all geographic regions.

Conclusions: Anaesthesia and especially sedation is frequently used during percutaneous cardiac procedures. The rate of use and perceptions regarding sedation differs among professionals and might be influenced by culture, training, and geography. There is a lack of adequate formal training in the use of sedation and analgesia for nonanaesthesia professionals.

(38 %) cardiologues des autres pays ($P < 0,0001$). L'utilisation de l'anesthésie générale au cours d'interventions complexes comme le remplacement valvulaire transaortique est également plus fréquente en Amérique du Nord (92 %) que dans les autres pays (76 %; $P = 0,004$). Une formation particulière sur la sédation a été offerte à moins d'un tiers des professionnels autres que les anesthésiologistes. Bien que plus de la moitié des infirmières et infirmiers aient reçu la formation sur la sédation procédurale, cette formation a été offerte à moins d'un quart des cardiologues. Le manque de formation a été noté dans toutes les régions géographiques.

Conclusions : L'anesthésie et particulièrement la sédation sont fréquemment utilisées durant les interventions cardiaques percutanées. Le taux d'utilisation et les points de vue sur la sédation diffèrent entre les professionnels et seraient influencés par la culture, la formation et la région géographique. Il manque de formation officielle adéquate sur l'utilisation de la sédation et de l'analgésie s'adressant aux professionnels autres que les anesthésiologistes.

Methods

Definitions

The definition of anaesthesia for this study was based on a position statement written by the Canadian Anesthesiologists' Society,[10] in which general anaesthesia was defined as "a state of total unconsciousness resulting from anaesthetic drug(s)," sedation as "a state of reduced excitement or anxiety that is induced by the administration of a sedative agent," and analgesia as a "reduction of, or insensibility to pain without loss of consciousness." Although the term, anaesthesia, also comprises local anaesthesia, for the purpose of the survey, unless specified, the term anaesthesia addressed general anaesthesia, sedation, and analgesia but did not address local anaesthesia per se, which might or might not have been used in many cases.

The American Society of Anesthesiologists established guidelines regarding moderate sedation/analgesia (conscious sedation), and monitored anaesthesia care.[11]

The provider of monitored anaesthesia care is qualified to use all anaesthesia resources to support life and provide patient comfort and safety during diagnostic and therapeutic procedures, and is prepared and qualified to convert to general anaesthesia when necessary.[11] Because most of the participants in the survey were not anaesthesia staff and might not be familiar with these definitions, for the purpose of this survey, we used the term, moderate sedation.

Survey

We designed a survey assessing anaesthesia practices during laboratory-based cardiac procedures. The questions addressed the type of practice, type of anaesthesia during different cardiac procedures, and the perceptions regarding anaesthesia. Questions included periprocedural use of the following drugs: benzodiazepines (sedative-hypnotics), fentanyl (opioid analgesic), propofol (sedative-hypnotic), remifentanil (opioid analgesic), morphine/hydromorphone (opioid analgesic), dexmedetomidine (sedative), or use of other narcotics.

We used the Internet-based software (Survey Monkey, Palo Alto, CA) to design and distribute the survey. In the development phase, 46 questions were written and then reduced to 32 structured-response format questions, to increase the likelihood of response.[12] In the pilot phase, the survey was sent to 15 individuals who provided comments regarding the relevance of the questions (face validity) and readability. The final version included 27 questions and was completed within 10 minutes by all pilot phase participants. E-mail invitations to participate in the survey were sent once by the following official societies: Canadian Association of Interventional Cardiology (212 invitations), Canadian Anesthesiologists' Society (1697 invitations), Canadian Heart Rhythm Society (118 invitations), and the Canadian Council of Cardiovascular Nurses (1265 invitations). Invitation e-mails were also sent to 608 participants in international investigator networks. The participants in the investigator networks received a reminder e-mail 3 weeks after the initial invitation. Participants in the investigator networks could also receive an invitation by one of the national societies if applicable. Because we could not identify those specifically involved with cardiac procedures within either the anesthesiologists society, or the nurses council, we requested that only those involved with cardiac procedures respond to the survey. Invitation e-mails described the survey, and provided an estimate of 10 minutes for survey completion and an incentive of optional participation in an iPad draw. The survey included single and multiple item questions and a progress indicator bar. Each participant was directed to answer only questions that were applicable to his/her practice. A copy of the survey is shown in Supplemental Appendix S1.

The survey took place from December 2012 to September 2013. Invitations were sent directly by the participating organizations after approval by each of the organizations. Access to the survey was available for each group of invitees for 2 months.

The Research Ethics Board of Western University approved the study, and a letter of information was attached to the invitation emails.

Data are descriptive. Values are reported as absolute values and/or percentages of the total number of responses. Results were analyzed according to geographic location and profession. Comparisons between groups were performed using the Fisher exact test.

Table 1. Type of anaesthesia reported in all participants' practices

	None	Sedation	General anaesthesia	Not done
Coronary angiography or PCI	115 (27.0)	214 (50.2)	5 (1.2)	92 (21.6)
ASD/PFO closure	21 (5.3)	71 (17.8)	103 (25.8)	205 (51.3)
Alcohol septal ablation	18 (4.6)	86 (21.7)	39 (9.9)	253 (63.9)
Mitral valvuloplasty	16 (4.1)	65 (16.5)	80 (20.3)	234 (59.2)
Aortic valvuloplasty	17 (4.3)	81 (20.5)	89 (22.5)	208 (52.7)
TAVI	11 (2.8)	23 (5.8)	152 (38.5)	209 (52.9)
Peripheral intervention	60 (15.0)	134 (33.6)	19 (4.8)	186 (46.6)
Carotid stenting	40 (10.1)	89 (22.4)	34 (8.5)	235 (59.1)
Pediatric cardiac catheterization	12 (3.1)	23 (5.8)	57 (14.5)	302 (76.7)
Ablation for atrial fibrillation	21 (5.1)	115 (28.0)	69 (16.8)	206 (50.1)
Other arrhythmia ablation	27 (6.5)	153 (37.1)	39 (9.4)	194 (47.0)
Transesophageal echocardiography	31 (7.4)	230 (54.9)	30 (7.2)	128 (30.6)
Pacemaker implantation	64 (14.9)	229 (53.1)	21 (4.9)	117 (27.2)

Numbers represent frequencies with percentages in parenthesis. None indicates sedation not given; not done, procedure not performed by survey responders.

ASD, atrial septal defect; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; TAVI, transcatheter aortic valve implantation.

Results

Demographic characteristics

Four hundred ninety-seven participants completed the survey. Most of the responders were from North America (67.8%), with 20.2% from Europe, 6.1% from South America, and 5.9% from other countries. A large proportion (63.9%) of the responders worked in academic or teaching hospitals, 27% in community hospitals, 8% in private hospitals, and 1% in other hospital settings. Cardiologists comprised 51.7% of the responders (the majority of whom [31.7%] were interventional cardiologists), anaesthesiologists 35.8%, and nurses 12.3%. The duration of practice among responders was: > 20 years (38.2%), 10-19 years (32.8%), 5-9 years (18%), and < 5 years (11%).

Table 2. Type of anaesthesia used by cardiologists

	None	Sedation	General anaesthesia	Not done
Interventional Cardiologist				
Coronary angiography or PCI	49 (32.5)	101 (66.9)	1 (0.7)	0 (0.0)
ASD/PFO closure	5 (3.7)	44 (32.1)	25 (18.3)	63 (46.0)
Alcohol septal ablation	2 (1.5)	47 (34.3)	16 (11.7)	72 (52.6)
Mitral valvuloplasty	5 (3.7)	40 (29.6)	11 (8.2)	79 (58.5)
Aortic valvuloplasty	8 (6.0)	47 (35.1)	13 (9.7)	66 (49.3)
TAVI	1 (0.7)	16 (11.8)	47 (34.6)	72 (52.9)
Peripheral intervention	26 (18.8)	37 (26.8)	1 (0.7)	74 (53.6)
Carotid stenting	22 (16.1)	21 (15.3)	1 (0.7)	93 (67.9)
Pediatric cardiac catheterization	3 (2.2)	11 (8.1)	16 (11.8)	108 (77.9)
Electrophysiologist				
Ablation for atrial fibrillation	0 (0.0)	17 (53.1)	10 (31.3)	5 (15.6)
Other arrhythmia ablation	2 (5.9)	29 (85.3)	1 (2.9)	2 (5.9)
Pacemaker implantation	4 (11.4)	27 (77.1)	2 (5.7)	2 (5.7)
General or noninvasive cardiologists				
Transesophageal echocardiography	11 (25.0)	27 (61.4)	2 (4.6)	4 (9.1)

Numbers represent frequencies with percentages in parenthesis. None indicates sedation not given; not done, procedure not performed by survey responders.

ASD, atrial septal defect; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; TAVI, transcatheter aortic valve implantation.

Type of sedation

Sedation is commonly used in patients who undergo nonsurgical cardiac procedures. The overall use of sedation or other forms of anaesthesia (except for local anaesthetics) by all survey participants is reported in Table 1. Anaesthetic use by relevant cardiology subgroups is reported in Table 2. The most common drugs used are benzodiazepines and fentanyl (Fig. 1A), particularly when nonanaesthesia personnel such as interventional cardiologists, provide sedation (Fig. 1B). Although benzodiazepines and fentanyl boluses are commonly used among anaesthesiologists as well, they also frequently use other drugs such as propofol or remifentanil infusions (Fig. 1C).

Sedation is used routinely by 77/84 (92%) of the cardiologists from North America who perform cardiac catheterization and PCI, but only by 46/121 (38%) of non-North American cardiologists who participated in the survey ($P < 0.0001$). During pacemaker implantation, sedation or general anaesthesia is provided by 44/44 (100%) of the cardiologists from North America, vs 57/102 of the cardiologists from other countries ($P < 0.0001$). One hundred seven of 116 (92%) of the participants in North America who are involved in TAVI procedures use general anaesthesia and 8% use sedation only. In contrast, 44/58 (76%) of the participants from other countries use general anaesthesia and 24% use sedation only ($P = 0.004$ compared with North America). Most of the participants who use sedation only during TAVI were from European countries (13/45; 29%; $P = 0.001$ compared with North America).

When sedation was used, 101/112 (90%) of the cardiologists from North America used benzodiazepines in more than half of their cases compared with 62/122 (51%) in other countries ($P < 0.0001$). Remifentanil is used sometimes by 15/92 (16%) in North America, but more frequently in other countries 29/96 (30%) ($P = 0.03$). Morphine is infrequently used by cardiologists in North America (28/92; 30%), and more frequently used elsewhere (64/106; 60%; $P < 0.0001$).

The decision to provide sedation is influenced by a number of factors, including physician (83.1%) and patient request (36.5%). Nurse preference might contribute to 8.9% and hospital policy to 20.2% of the total percentage of sedation use. Physician (81.4%) and patient (35.3%) preferences are also the main reasons for not providing sedation. Shortage of human resources or costs might contribute to 13% or 1.3%, respectively, to a lack of procedural sedation administration. Anaesthesia professionals such as anaesthesiologists, nurse anaesthetists, or anaesthesia assistants are available to provide conscious sedation in only 45.4% of the centres in which the participants worked.

Perception regarding sedation

The perception regarding a patient's desire to receive sedation during simple cardiac procedures such as cardiac

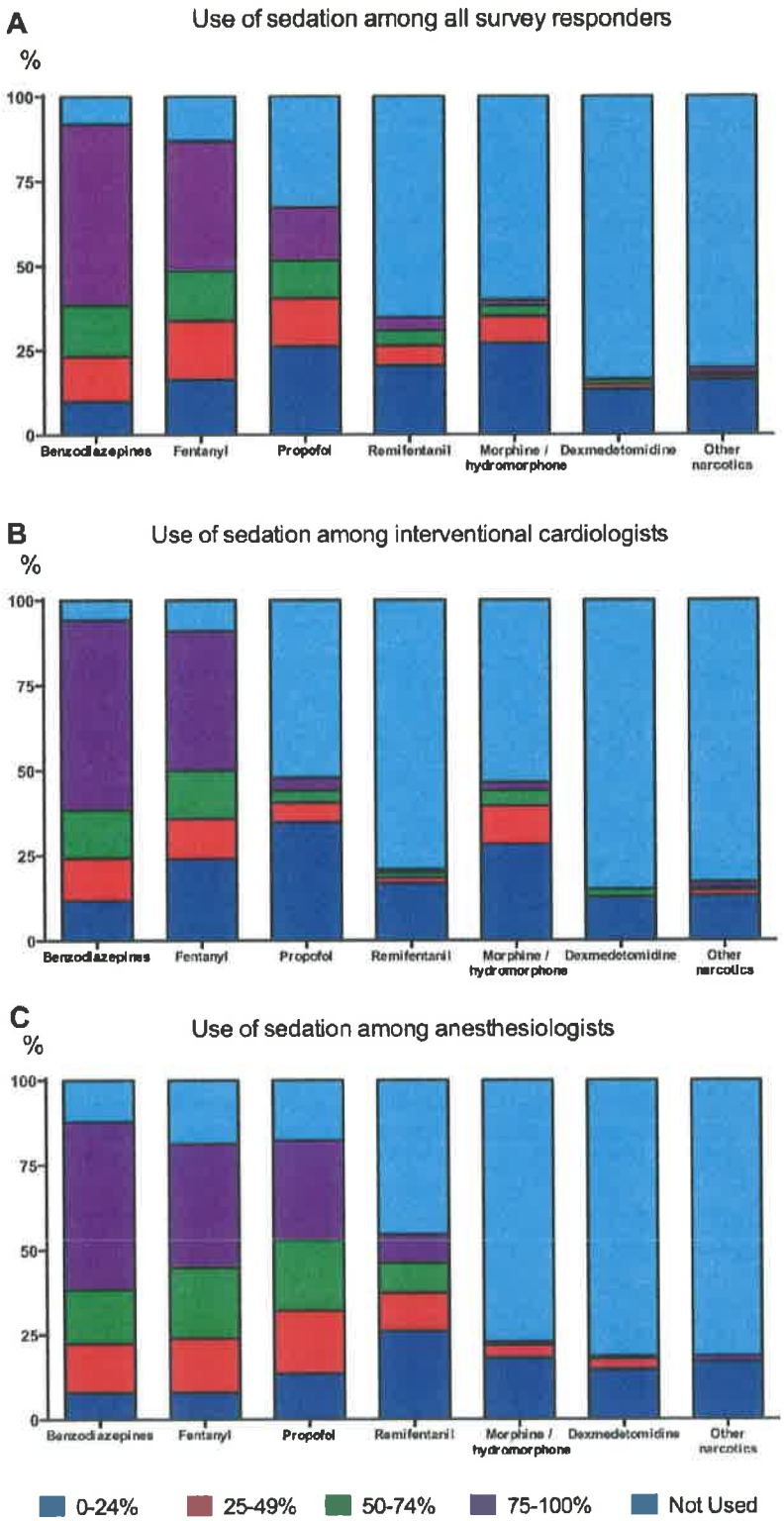

Figure 1. Frequency of sedative medication use. (**A**) All survey participants; (**B**) interventional cardiologists; and (**C**) anaesthesiologists.

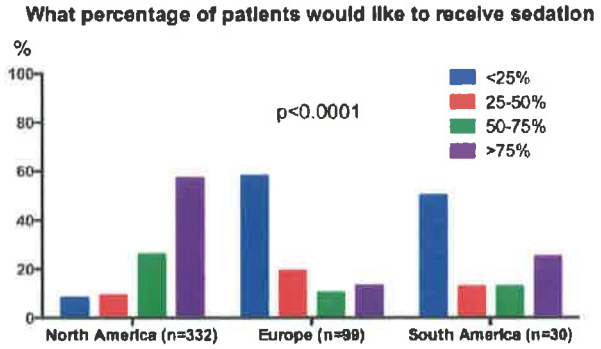

Figure 2. Medical professional staff perception of patients' desire to receive sedation according to region.

catheterization differs between regions (Fig. 2). Forty-five of 50 (90%) of the nurses believe that most patients would like sedation for cardiac catheterization, vs 95/128 (74%) of anaesthesiologists and 88/157 (56%) of interventional and invasive cardiologists ($P < 0.0001$). Among the participants from North America, 43/46 (93%) of nurses, 91/118 (77%) of anaesthesiologists, and 90/107 (84)% of cardiologists believed that more than 50% of the patients would like to receive sedation ($P = 0.04$). The radial artery is more prone to spasm during cardiac catheterization compared with the femoral artery. It was thought that sedation decreases radial artery spasm.[13] Indeed, among interventional cardiologists, 29.4% believe that more sedation should be given when the procedure is performed via the radial approach, as opposed to 4.6% who thought that more sedation should be given when the femoral approach is used. Regardless of vascular approach, a similar proportion was given sedation (41.2%).

Training

Sedation-related training was provided only to 29.7% of nonanaesthesiologists. Only a minority of cardiologists who performed invasive procedures received training for procedural sedation: 21.1% of interventional cardiologists and 18.9% of electrophysiologists; and nurses reported higher proportion of sedation-related training (52.5%). Training was infrequent among cardiologists in all regions. In North America, 25/112 (31%) of the cardiologists received specific training for sedation compared with 35/132 (27%) of the cardiologists in other countries ($P = 0.46$). In Europe, 12/84 (14%) of the cardiologists reported receiving such training ($P = 0.2$ compared with North America).

Despite this low level of training, 70% of interventional cardiologists believed that they should monitor sedation during cardiac catheterization and PCI procedures that they perform.

Most participants from North America (81%) would like to receive sedation if they require a cardiac procedure themselves, but only 51% of the European participants and 58% of the participants from South America would like to receive sedation in such a case. Among North American participants, 85% of cardiologists, 75% of anaesthesiologists, and 89% of nurses would like to receive sedation themselves if they had to undergo a cardiac procedure.

Although it is common for nurses to be responsible for mild sedation, 41.9% of all responders reported that nurses also provide moderate sedation (response to verbal stimuli) and 7.4% reported that nurses provide deep sedation as well.

Discussion

To our knowledge, this is the largest survey published to date, to address anaesthesia practices during laboratory-based cardiac procedures. The principal findings of our survey were: (1) anaesthesia (mainly sedation) is commonly used during percutaneous cardiac procedures; (2) there is geographic variation in the type and use of sedation for cardiac procedures; general anaesthesia and overall sedation use is greater in North America compared with in Europe; (3) the perception regarding sedation differs among medical professions, and can be influenced by culture and geography; and (4) most of the nonanaesthesia professionals who provided moderate sedation did not receive specific training related to sedation.

Practice preferences according to region

Although anaesthesia might be viewed as an integral part of cardiac procedures, interestingly, there is not much information regarding sedation-related practice patterns. To our knowledge, our study is the largest and broadest international survey performed so far to investigate sedation during cardiac procedures. We found that sedation is frequently used with various types of cardiac procedures. The high use of sedation according to our survey might reflect the fact that most of the responders to the survey were from North America, where we found that the use of sedation is very common. Similarly, a previous report demonstrated higher use of sedation in North America compared with Europe in patients treated for acute respiratory failure.[14] North American participants reported high use of sedation during simple procedures such as cardiac catheterization, and more universal sedative use for other procedures such as pacemaker implantation. For complex procedures such as TAVI, our findings were similar to a recent report: in North America general anaesthesia is the standard practice.[15] In Europe, conscious sedation is considered an alternative, although general anaesthesia is still the preferred approach in this type of procedure. The frequent use of sedation in North America might reflect a perception of medical professionals that their patients would like to be sedated during cardiac procedures. We did not contact patients to receive their actual preference and therefore our study reflects only the medical professional perspective. However, we found that responders from North America were more likely to request sedation for themselves, if they would require a cardiac procedure. Unfortunately, this desire to follow personal attitude is not accompanied by following established guidelines for administration of sedation.[16] Participants from Europe reported receiving less sedation-related training compared with responders from North America. Although less training might result in a decreased desire to use sedation, it

might also reflect less interest in using sedation, which might be perceived as an unnecessary intervention.

Practice preferences according to sedation drugs

Most North American cardiologists use benzodiazepines in most of their cases compared with approximately half of the European and South American cardiologists. The most frequent opioid used is fentanyl. The combination of midazolam and fentanyl was popular among nonanaesthesia personnel in our survey. Remifentanil and dexmedetomidine were more frequently used in Europe than in North America. These drugs, and propofol, are used mainly by anaesthesia personnel in North America for sedation.

Preferences according to medical profession

We found that nurses viewed sedation as an integral part of cardiac procedures whereas although the cardiologists who perform the procedures decide if the patients receive sedation, they often view sedation as less needed. The differences between professions were similar whether the intended use of sedation was for patients or for themselves if they become ill. However, much of the difference between professions in our study was related to geography, and differences were less marked between professions when we restricted the analysis to responders from North America. The question of who needs to monitor anaesthesia has important clinical and legal implications. Although one might argue that nonanaesthesia professionals can perform such a task, sedation might lead to serious complications requiring airway management, especially when nonanaesthesia professionals provide moderate sedation. In fact, some states restrict certain types of sedation, such as using propofol, for use by anaesthesia professionals only,[17] and according to the remifentanil product monograph this medication should be used only by individuals who received specific training in the use of anaesthetic drugs including airway management and assisted ventilation. Importantly, most participants reported that anaesthesia professionals are not available in their institution to provide conscious sedation.

Sedation training among nonanaesthesia professionals

When nonanaesthesia professionals provide and monitor sedation, one would expect that they receive the required training. Guidelines for sedation and anaesthesia by nonanaesthesiologists were developed by the American Society of Anaesthesiologists with input from nonanaesthesia experts and were endorsed by different societies.[16,18] Surprisingly, we found that despite the cardiologists' perspective that they can monitor the sedation themselves, most did not receive the required relevant training. The lack of training was found across different nonanaesthesia personnel and across all geographic areas investigated. This finding is worrisome because the potential for airway complications is high, especially when moderate to deep sedation is given. Further, often despite the intention to provide light sedation, the result is a deeper level in which the patient falls asleep (Ramsay sedation scale ≥ 4).[10] At this level of sedation, monitoring with capnography is recommended. Although the survey did not include questions about such monitoring, it seems that such monitoring is not routinely available in all labs. Further quality improvement projects are required to address this important issue.

Based on our findings, it seems that there is a need to either increase the number of available anaesthesia professionals who can safely provide monitored anaesthesia care, or to provide relevant training to other professionals. We suggest that formal training in sedation, including airway management, should be mandatory for cardiologists and nurses who administer sedation, and greater availability of anaesthesia staff for percutaneous cardiac procedures be considered.

Limitations

International participants in the survey were approached via research networks, and therefore our results might be more reflective of academic institutions that are involved in research. We tried to minimize such bias by inviting members of other professional organizations. However, participants in such organizations, and particularly those who respond to a survey, might be more likely to have an academic interest. Further, involvement of Canadian national societies led to a higher participation from North America. Because we did not have direct access to e-mail addresses of participants, invitations were sent by the participating societies only once. The response rate was greater among cardiologists compared with anaesthesiologists and nurses. Therefore, the validity of the results obtained from the cardiologists might be greater. The lower response rate among anaesthesiologists and nurses raises the possibility that respondents are different from nonresponders.[12] This is likely, because we requested and expected that only individuals who have a role in cardiac procedures would respond to the survey.

Some of the questions of the survey were related to perspectives of team members on patients' expectations. Although those perspectives might be related to the ultimate rate of use of sedation, they do not represent actual patients' opinions, because patients were not included in the survey. Although assessment of degree of anaesthesia for a specific patient might be better assessed using a scale, such as the Ramsay Sedation Scale, we preferred to use more general terms such as moderate sedation in the questionnaire, to obtain the participant perspective.

Monitored anaesthesia care includes a variety of postprocedure responsibilities beyond the expectations of practitioners who provide moderate sedation.[11] Thus, detailed types of medications with regard to each of the procedures and monitored anaesthesia care are beyond the scope of this survey.

We did not address in the survey the technique of administering local anaesthesia. An effective local anaesthesia application might reduce the need for sedation, and should be considered as part of the anaesthesia training for cardiologists.

Acknowledgements

We are grateful to the scientific societies and research organizations that helped us in connecting with their members and to the participants in the survey.

Funding Sources

This work was supported by the Program of Experimental Medicine in the Department of Medicine, Western University.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.03.034.